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#3
Title: PROTEASE INHIBITOR PEPTIDES
Inventor(s): R. Tyler WHITE et. al
Serial No. 10/076,604
DOCKET NO.: 056324-0129

FIG. 1

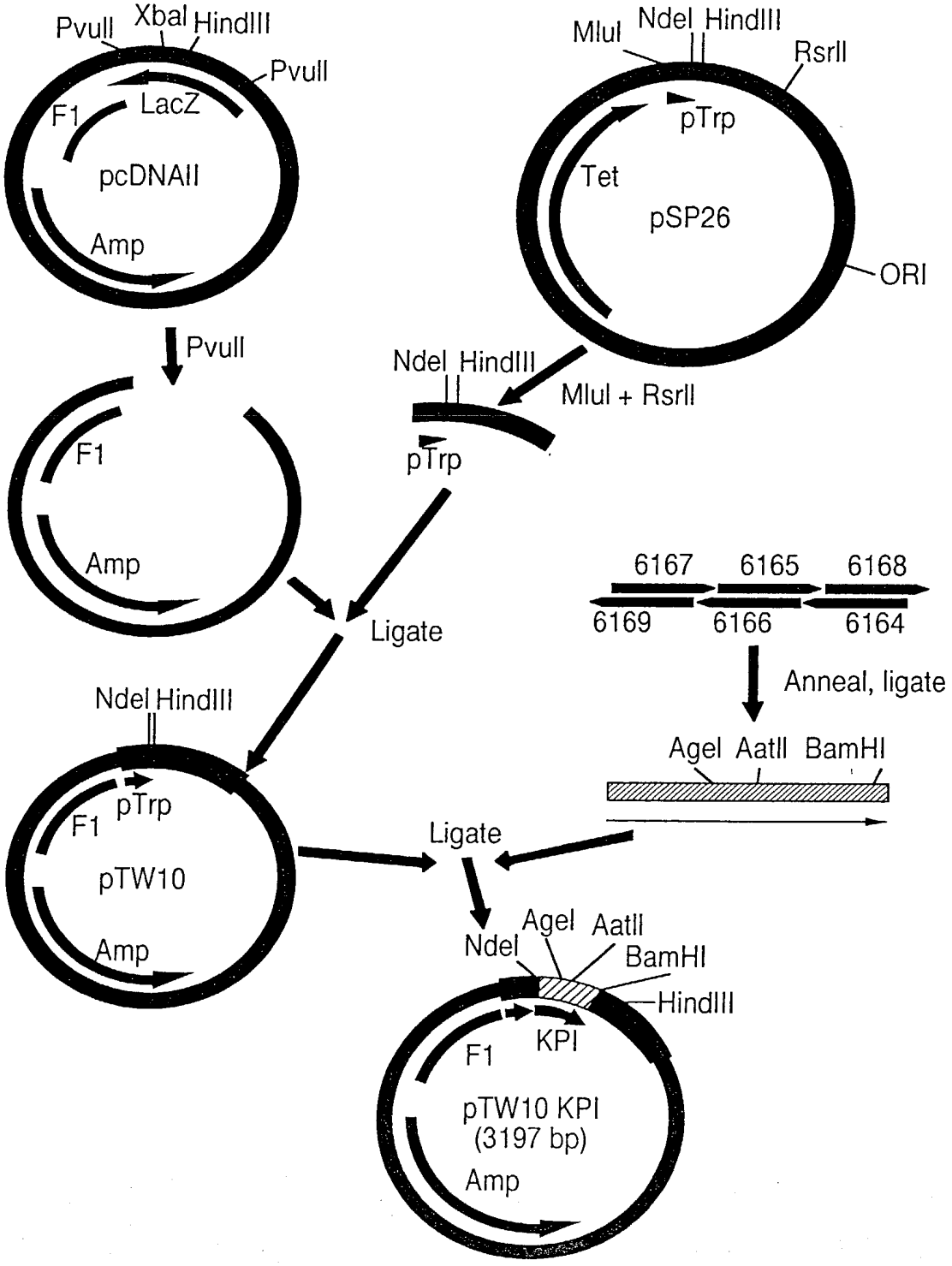

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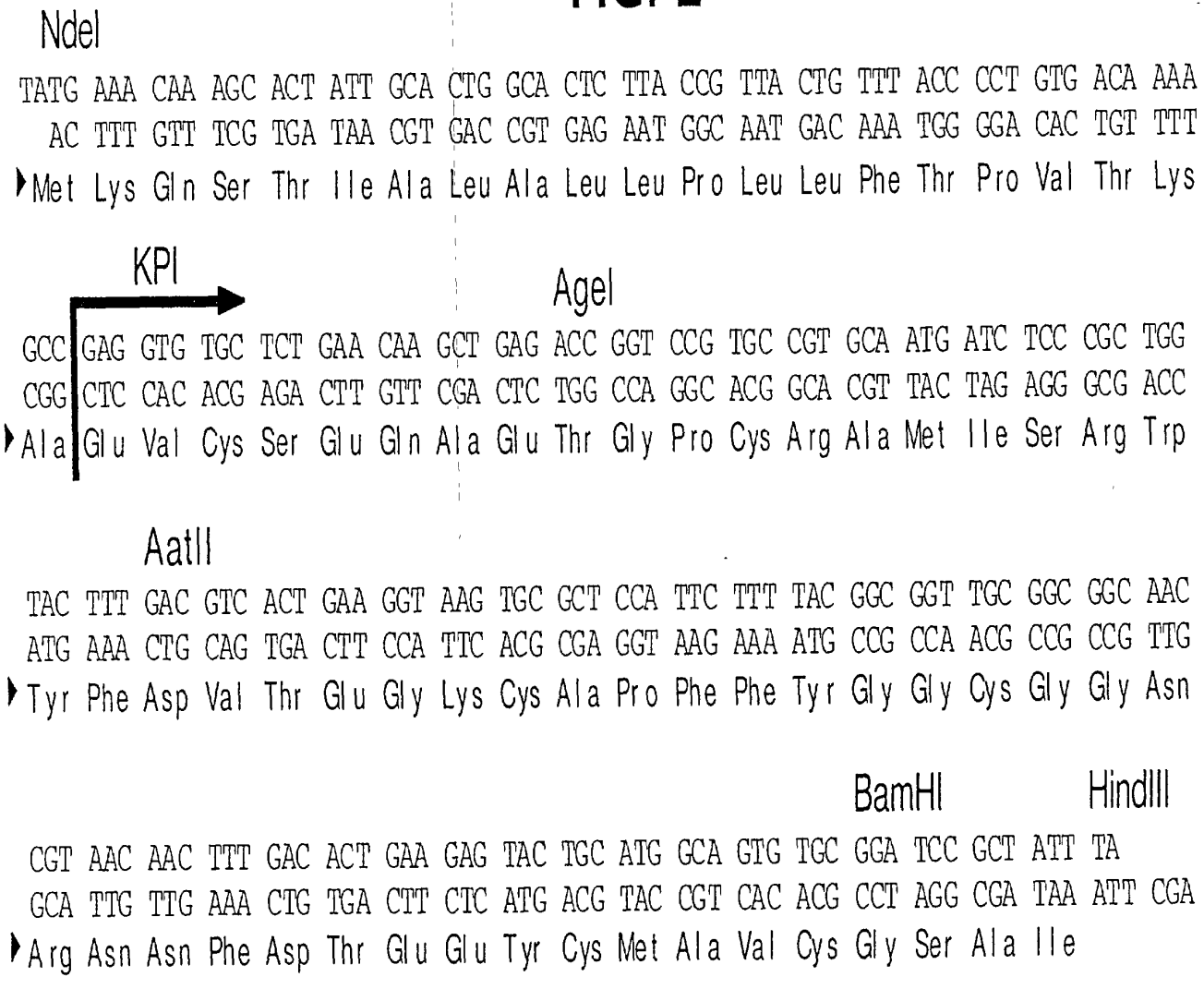
FIG. 2



Title: PROTEASE INHIBITOR PEPTIDES
Inventor(s): R. Tyler WHITE et. al
Serial No. 10/076,604
DOCKET NO.: 056324-0129

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Title: PROTEASE INHIBITOR PEPTIDES
Inventor(s): R. Tyler WHITE et. al
Serial No. 10/076,604
DOCKET NO.: 056324-0129

FIG. 3

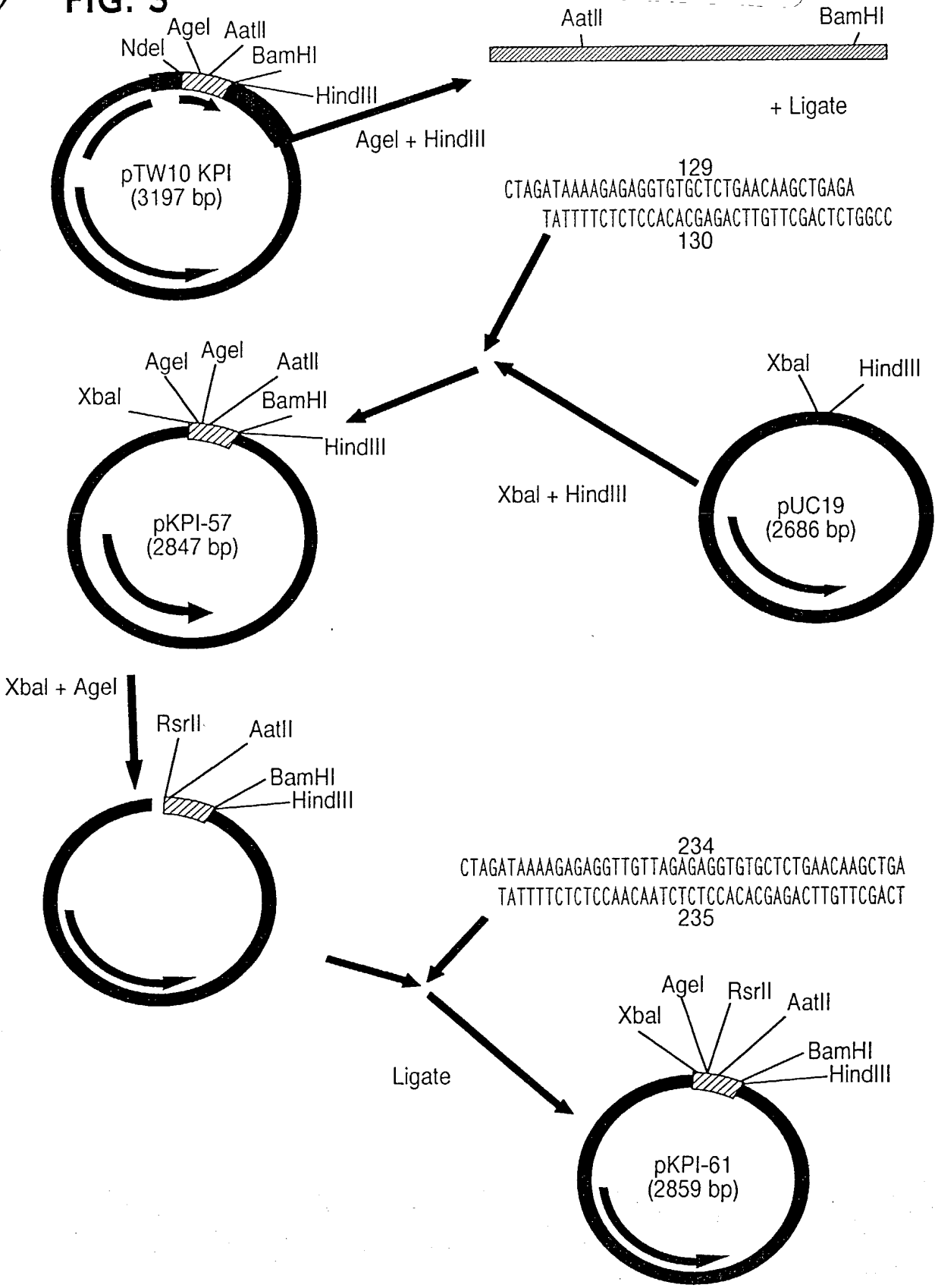

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FIG. 4

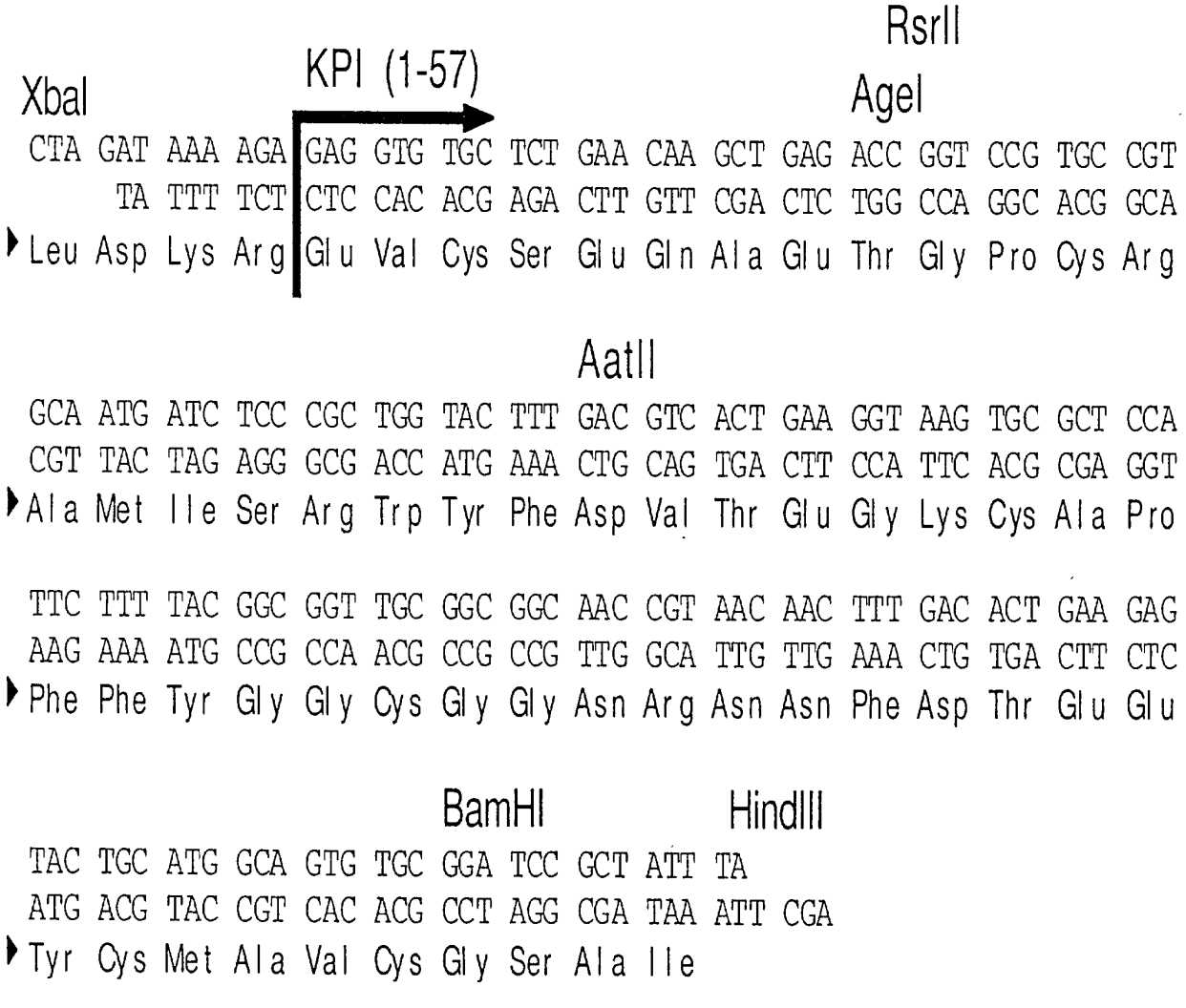

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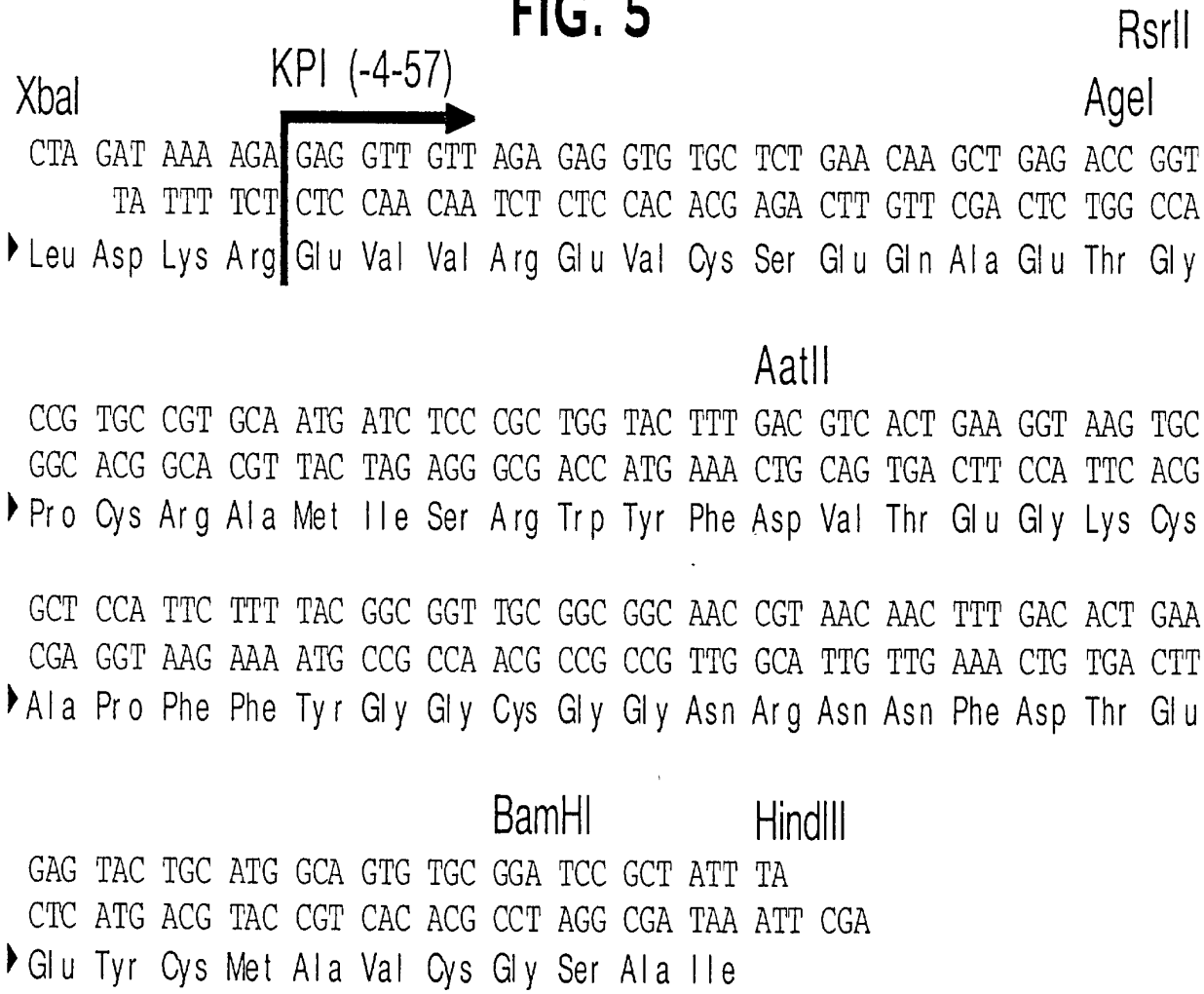
FIG. 5



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DOCKET NO.: 056324-0129

FIG. 6

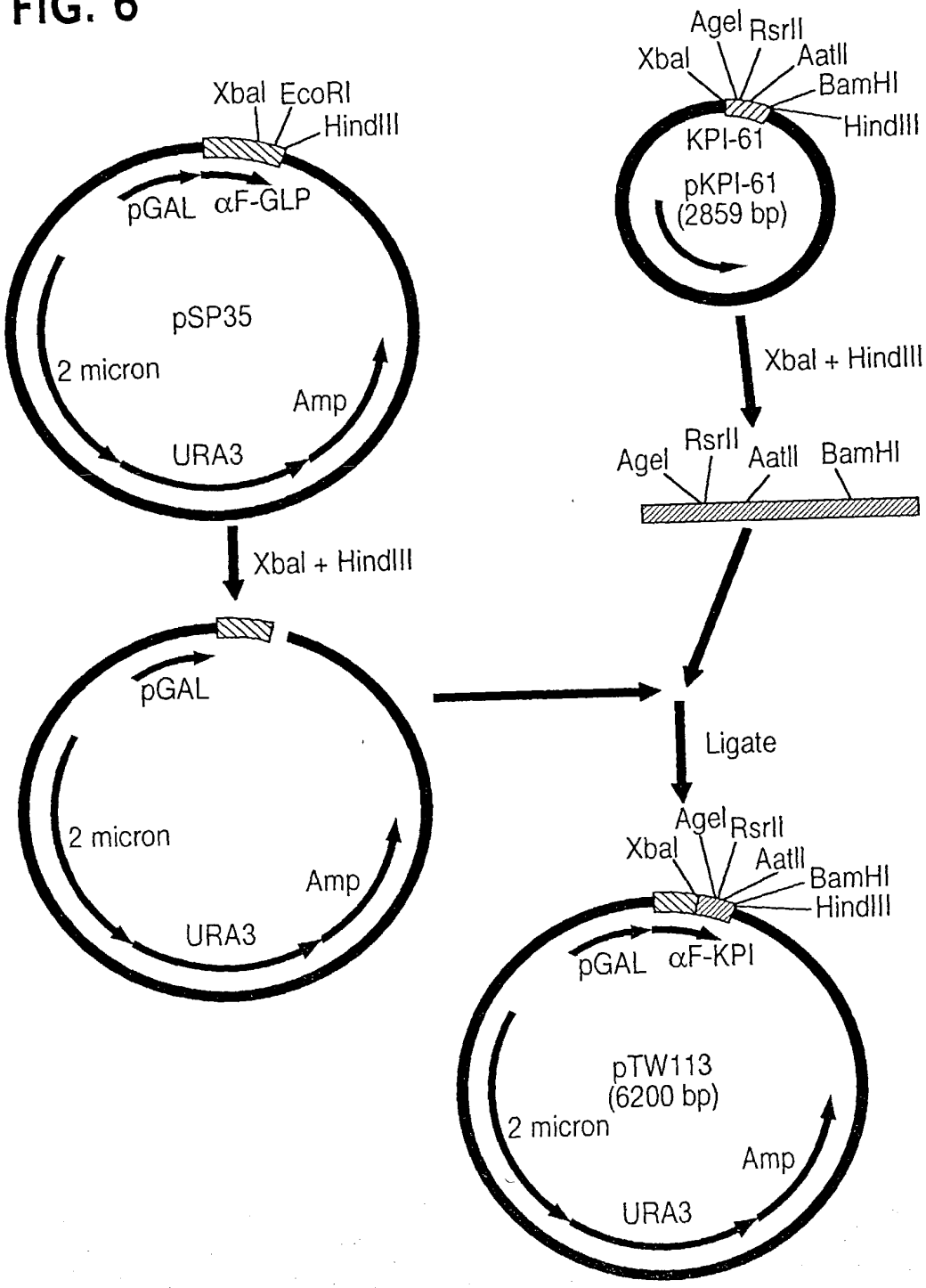

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FIG. 7

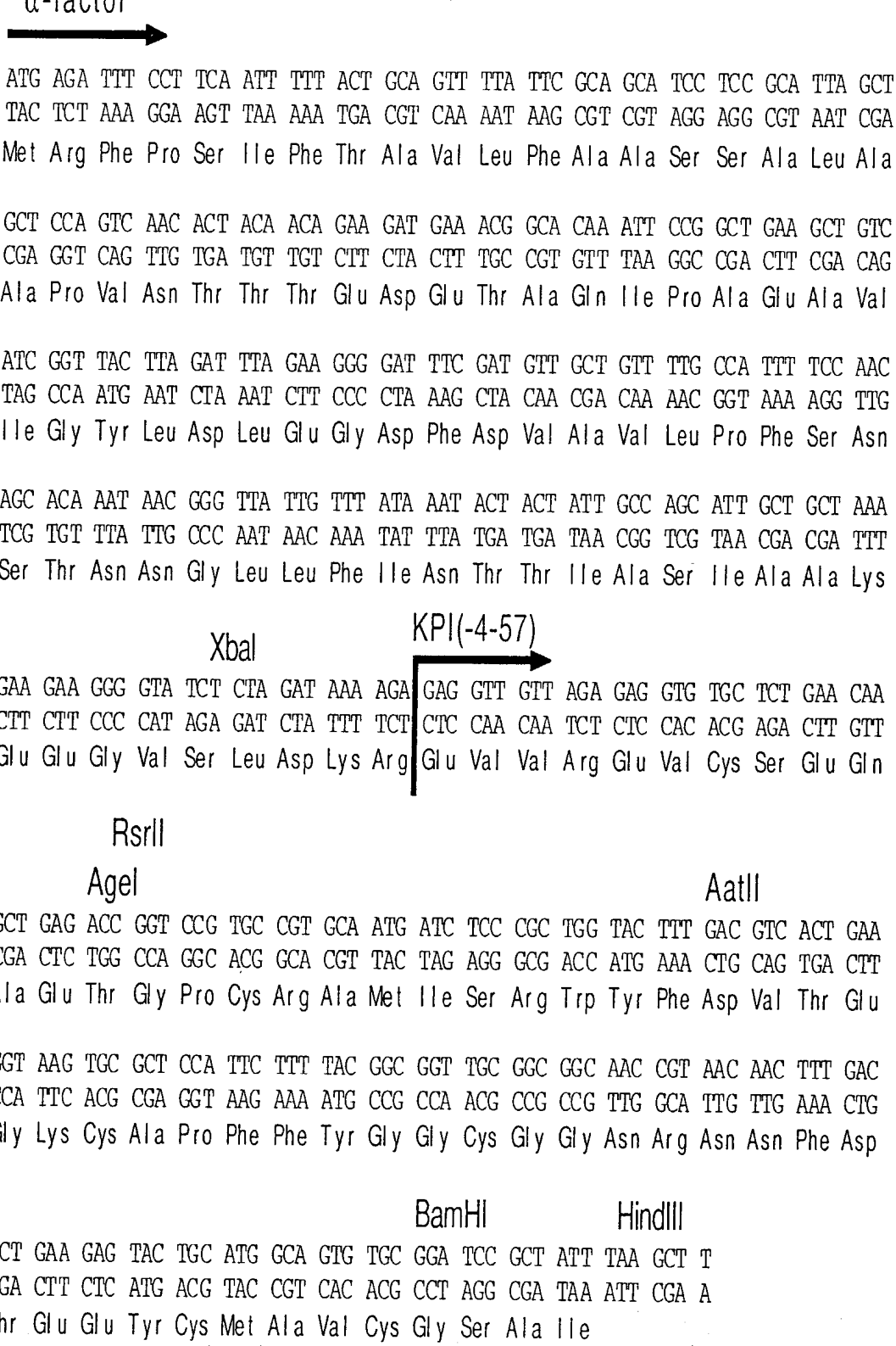

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FIG. 8

KPI(-4-57)

Glu	Val	Val	Arg	Glu	Val	Cys	Ser	Glu	Gln	Ala
-4	-3	-2	-1	1	2	3	4	5	6	7

Glu	Thr	Gly	Pro	Cys	Arg	Ala	Met	Ile	Ser	Arg
8	9	10	11	12	13	14	15	16	17	18

Trp	Tyr	Phe	Asp	Val	Thr	Glu	Gly	Lys	Cys	Ala
19	20	21	22	23	24	25	26	27	28	29

Pro	Phe	Phe	Tyr	Gly	Gly	Cys	Gly	Gly	Asn	Arg
30	31	32	33	34	35	36	37	38	39	40

Asn	Asn	Phe	Asp	Thr	Glu	Glu	Tyr	Cys	Met	Ala
41	42	43	44	45	46	47	48	49	50	51

Val	Cys	Gly	Ser	Ala	Ile
52	53	54	55	56	57

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FIG. 9

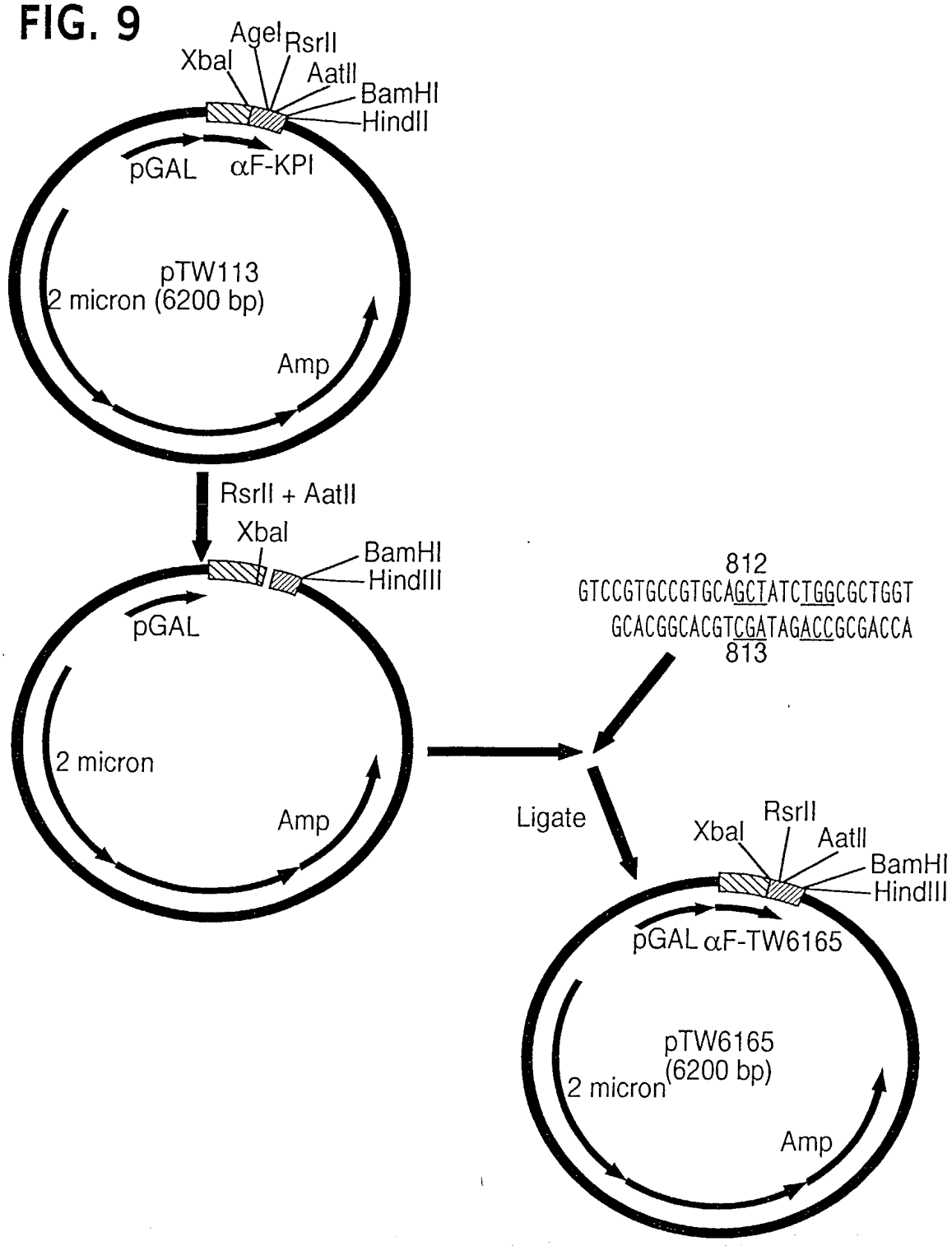

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FIG. 10

pTW 6165

α-factor →

```
ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA
Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG
Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG
Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT
Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys
```

XbaI — KPI(-4-57; M15A, S17W) →

```
GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT
Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln
```

RsrII — AgeI — AatII

```
GCT GAG ACC GGT CCG TGC CGT GCA GCT ATC TGG CGC TGG TAC TTT GAC GTC ACT GAA
CGA CTC TGG CCA GGC ACG GCA CGT CGA TAG ACC GCG ACC ATG AAA CTG CAG TGA CTT
Ala Glu Thr Gly Pro Cys Arg Ala Ala Ile Trp Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG
Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp
```

BamHI — HindIII

```
ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A
Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile
```

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FIG. 11

812
GTCCGTGCCGTGCAGCTATCTGGCGCTGGTACTTTGACGT
GCACGGCACGTCGATAGACCGCGACCATGAAAC
813

814
GTCCGTGCCGTGCAGCTATCTACCGCTGGTACTTTGACGT
GCACGGCACGTCGATAGATGGCGACCATGAAAC
815

867
GTCCGTGCCGTGCATTGATCTTCCGCTGGTACTTTGACGT
GCACGGCACGTAACTAGAAGGCGACCATGAAAC
868

1493
GTCCGTGCCGTGCATTGATCTACCGCTGGTACTTTGACGT
GCACGGCACGTAACTAGATGGCGACCATGAAAC
1494

925
GTCCGTGCCGTGCAATGCACTTCCGCTGGTACTTTGACGT
GCACGGCACGTTACGTGAAGGCGACCATGAAAC
926

927
GTCCGTGCCGTGCAATGCACTACCGCTGGTACTTTGACGT
GCACGGCACGTTACGTGATGGCGACCATGAAAC
928

929
GTCCGTGCCGTGCAATGCACTGGCGCTGGTACTTTGACGT
GCACGGCACGTTACGTGACCGCGACCATGAAAC
930

863
GTCCGTGCCGTGCAGCTCACTCCCGCTGGTACTTTGACGT
GCACGGCACGTCGAGTGAGGGCGACCATGAAAC
864

865
GTCCGTGCCGTGCATTGCACTCCCGCTGGTACTTTGACGT
GCACGGCACGTAACGTGAGGGCGACCATGAAAC
866

pTW6165 KPI(-4-57; M15A, S17F)

pTW6166 KPI(-4-57; M15A, S17Y)

pTW6175 KPI(-4-57; M15L, S17F)

pBG028 KPI(-4-57; M15L, S17Y)

pTW6183 KPI(-4-57; I16H, S17F)

pTW6184 KPI(-4-57; I16H, S17Y)

pTW6185 KPI(-4-57; I16H, S17W)

pTW6173 KPI(-4-57; M15A, I16H)

pTW6174 KPI(-4-57; M15L, I16H)

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pTW 6166

FIG. 12

α-factor →

```
ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA
Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG
Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG
Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT
Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys
```

XbaI — KPI(-4-57; M15A, S17Y) →

```
GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT
Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln
```

RsrII
AgeI — AatII

```
GCT GAG ACC GGT CCG TGC CGT GCA GCT ATC TAC CGC TGG TAC TTT GAC GTC ACT GAA
CGA CTC TGG CCA GGC ACG GCA CGT CGA TAG ATG GCG ACC ATG AAA CTG CAG TGA CTT
Ala Glu Thr Gly Pro Cys Arg Ala Ala Ile Tyr Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG
Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp
```

BamHI — HindIII

```
ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A
Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile
```

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FIG. 13

pTW 6175

α-factor

```
ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA
Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG
Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG
Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT
Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys
```

XbaI — KPI(-4-57; M15L, S17F)

```
GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT
Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln
```

RsrII

AgeI — AatII

```
GCT GAG ACC GGT CCG TGC CGT GCA TTG ATC TTC CGC TGG TAC TTT GAC GTC ACT GAA
CGA CTC TGG CCA GGC ACG GCA CGT AAC TAG AAG GCG ACC ATG AAA CTG CAG TGA CTT
Ala Glu Thr Gly Pro Cys Arg Ala Leu Ile Phe Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG
Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp
```

BamHI — HindIII

```
ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A
Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile
```

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FIG. 14

pBG028

α-factor

```
ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA
Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG
Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG
Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT
Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys
```

XbaI — KPI(-4-57; M15L, S17Y) →

```
GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT
Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln
```

RsrII — AgeI — AatII

```
GCT GAG ACC GGT CCG TGC CGT GCA TTG ATC TAC CGC TGG TAC TTT GAC GTC ACT GAA
CGA CTC TGG CCA GGC ACG GCA CGT AAC TAG ATG GCG ACC ATG AAA CTG CAG TGA CTT
Ala Glu Thr Gly Pro Cys Arg Ala Leu Ile Tyr Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG
Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp
```

BamHI — HindIII

```
ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A
Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile
```

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FIG. 15

pTW6183

α-factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA
Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG
Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG
Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT
Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys

XbaI

KPI(-4-57; I16H, S17F)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT
Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

RsrII

AgeI

AatII

GCT GAG ACC GGT CCG TGC CGT GCA ATG CAC TTC CGC TGG TAC TTT GAC GTC ACT GAA
CGA CTC TGG CCA GGC ACG GCA CGT TAC GTG AAG GCG ACC ATG AAA CTG CAG TGA CTT
Ala Glu Thr Gly Pro Cys Arg Ala Met His Phe Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG
Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A
Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile

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DOCKET NO.: 056324-0129

pTW6184

FIG. 16

α-factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA
Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG
Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG
Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT
Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys

XbaI

KPI(-4-57; I16H, S17Y)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT
Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

RsrII

AgeI

AatII

GCT GAG ACC GGT CCG TGC CGT GCA ATG CAC TAC CGC TGG TAC TTT GAC GTC ACT GAA
CGA CTC TGG CCA GGC ACG GCA CGT TAC GTG ATG GCG ACC ATG AAA CTG CAG TGA CTT
Ala Glu Thr Gly Pro Cys Arg Ala Met His Tyr Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG
Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A
Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile

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Inventor(s): R. Tyler WHITE et. al
Serial No. 10/076,604
DOCKET NO.: 056324-0129

pTW6185

FIG. 17

α-factor →

```
ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA
▸Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG
▸Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG
▸Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT
▸Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys
```

XbaI — KPI(-4-57; I16H, S17W) →

```
GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT
▸Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln
```

RsrII
AgeI — AatII

```
GCT GAG ACC GGT CCG TGC CGT GCA ATG CAC TGG CGC TGG TAC TTT GAC GTC ACT GAA
CGA CTC TGG CCA GGC ACG GCA CGT TAC GTG ACC GCG ACC ATG AAA CTG CAG TGA CTT
▸Ala Glu Thr Gly Pro Cys Arg Ala Met His Trp Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG
▸Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp
```

BamHI — HindIII

```
ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A
▸Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile
```

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Inventor(s): R. Tyler WHITE et. al
Serial No. 10/076,604
DOCKET NO.: 056324-0129

pTW6173

FIG. 18

α-factor

```
ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA
Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG
Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG
Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT
Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys
```

XbaI — KPI(-4-57; M15A, I16H)

```
GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT
Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln
```

RsrII — AgeI — AatII

```
GCT GAG ACC GGT CCG TGC CGT GCA GCT CAC TCC CGC TGG TAC TTT GAC GTC ACT GAA
CGA CTC TGG CCA GGC ACG GCA CGT CGA GTG AGG GCG ACC ATG AAA CTG CAG TGA CTT
Ala Glu Thr Gly Pro Cys Arg Ala Ala His Ser Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG
Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp
```

BamHI — HindIII

```
ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A
Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile
```

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pTW6174

FIG. 19

α-factor

```
ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA
Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG
Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG
Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT
Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys
```

XbaI — KPI(-4-57; M15L, I16H)

```
GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT
Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln
```

RsrII — AgeI — AatII

```
GCT GAG ACC GGT CCG TGC CGT GCA TTG CAC TCC CGC TGG TAC TTT GAC GTC ACT GAA
CGA CTC TGG CCA GGC ACG GCA CGT AAC GTG AGG GCG ACC ATG AAA CTG CAG TGA CTT
Ala Glu Thr Gly Pro Cys Arg Ala Leu His Ser Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG
Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp
```

BamHI — HindIII

```
ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A
Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile
```

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Title: PROTEASE INHIBITOR PEPTIDES
Inventor(s): R. Tyler WHITE et. al
Serial No. 10/076,604
DOCKET NO.: 056324-0129

FIG. 20

KPI(-4-57; M15A, S17W) TW6165

Glu	Val	Val	Arg	Glu	Val	Cys	Ser	Glu	Gln	Ala
-4	-3	-2	-1	1	2	3	4	5	6	7

Glu	Thr	Gly	Pro	Cys	Arg	Ala	Ala	Ile	Trp	Arg
8	9	10	11	12	13	14	15	16	17	18

Trp	Tyr	Phe	Asp	Val	Thr	Glu	Gly	Lys	Cys	Ala
19	20	21	22	23	24	25	26	27	28	29

Pro	Phe	Phe	Tyr	Gly	Gly	Cys	Gly	Gly	Asn	Arg
30	31	32	33	34	35	36	37	38	39	40

Asn	Asn	Phe	Asp	Thr	Glu	Glu	Tyr	Cys	Met	Ala
41	42	43	44	45	46	47	48	49	50	51

Val	Cys	Gly	Ser	Ala	Ile
52	53	54	55	56	57

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FIG. 21

KPI(-4-57; M15A, S17Y) TW6166

Glu	Val	Val	Arg	Glu	Val	Cys	Ser	Glu	Gln	Ala
-4	-3	-2	-1	1	2	3	4	5	6	7

Glu	Thr	Gly	Pro	Cys	Arg	Ala	Ala	Ile	Tyr	Arg
8	9	10	11	12	13	14	15	16	17	18

Trp	Tyr	Phe	Asp	Val	Thr	Glu	Gly	Lys	Cys	Ala
19	20	21	22	23	24	25	26	27	28	29

Pro	Phe	Phe	Tyr	Gly	Gly	Cys	Gly	Gly	Asn	Arg
30	31	32	33	34	35	36	37	38	39	40

Asn	Asn	Phe	Asp	Thr	Glu	Glu	Tyr	Cys	Met	Ala
41	42	43	44	45	46	47	48	49	50	51

Val	Cys	Gly	Ser	Ala	Ile
52	53	54	55	56	57

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FIG. 22

KPI(-4-57; M15L, S17F) TW6175

Glu	Val	Val	Arg	Glu	Val	Cys	Ser	Glu	Gln	Ala
-4	-3	-2	-1	1	2	3	4	5	6	7

Glu	Thr	Gly	Pro	Cys	Arg	Ala	Leu	Ile	Phe	Arg
8	9	10	11	12	13	14	15	16	17	18

Trp	Tyr	Phe	Asp	Val	Thr	Glu	Gly	Lys	Cys	Ala
19	20	21	22	23	24	25	26	27	28	29

Pro	Phe	Phe	Tyr	Gly	Gly	Cys	Gly	Gly	Asn	Arg
30	31	32	33	34	35	36	37	38	39	40

Asn	Asn	Phe	Asp	Thr	Glu	Glu	Tyr	Cys	Met	Ala
41	42	43	44	45	46	47	48	49	50	51

Val	Cys	Gly	Ser	Ala	Ile
52	53	54	55	56	57

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FIG. 23

KPI(-4-57; M15L, S17Y) BG028

Glu	Val	Val	Arg	Glu	Val	Cys	Ser	Glu	Gln	Ala
-4	-3	-2	-1	1	2	3	4	5	6	7

Glu	Thr	Gly	Pro	Cys	Arg	Ala	Leu	Ile	Tyr	Arg
8	9	10	11	12	13	14	15	16	17	18

Trp	Tyr	Phe	Asp	Val	Thr	Glu	Gly	Lys	Cys	Ala
19	20	21	22	23	24	25	26	27	28	29

Pro	Phe	Phe	Tyr	Gly	Gly	Cys	Gly	Gly	Asn	Arg
30	31	32	33	34	35	36	37	38	39	40

Asn	Asn	Phe	Asp	Thr	Glu	Glu	Tyr	Cys	Met	Ala
41	42	43	44	45	46	47	48	49	50	51

Val	Cys	Gly	Ser	Ala	Ile
52	53	54	55	56	57

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FIG. 24

KPI(-4-57; I16H, S17F) TW6183

Glu	Val	Val	Arg	Glu	Val	Cys	Ser	Glu	Gln	Ala
-4	-3	-2	-1	1	2	3	4	5	6	7

Glu	Thr	Gly	Pro	Cys	Arg	Ala	Met	His	Phe	Arg
8	9	10	11	12	13	14	15	16	17	18

Trp	Tyr	Phe	Asp	Val	Thr	Glu	Gly	Lys	Cys	Ala
19	20	21	22	23	24	25	26	27	28	29

Pro	Phe	Phe	Tyr	Gly	Gly	Cys	Gly	Gly	Asn	Arg
30	31	32	33	34	35	36	37	38	39	40

Asn	Asn	Phe	Asp	Thr	Glu	Glu	Tyr	Cys	Met	Ala
41	42	43	44	45	46	47	48	49	50	51

Val	Cys	Gly	Ser	Ala	Ile
52	53	54	55	56	57

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FIG. 25

KPI(-4-57; I16H, S17Y) TW6184

Glu	Val	Val	Arg	Glu	Val	Cys	Ser	Glu	Gln	Ala
-4	-3	-2	-1	1	2	3	4	5	6	7

Glu	Thr	Gly	Pro	Cys	Arg	Ala	Met	His	Tyr	Arg
8	9	10	11	12	13	14	15	16	17	18

Trp	Tyr	Phe	Asp	Val	Thr	Glu	Gly	Lys	Cys	Ala
19	20	21	22	23	24	25	26	27	28	29

Pro	Phe	Phe	Tyr	Gly	Gly	Cys	Gly	Gly	Asn	Arg
30	31	32	33	34	35	36	37	38	39	40

Asn	Asn	Phe	Asp	Thr	Glu	Glu	Tyr	Cys	Met	Ala
41	42	43	44	45	46	47	48	49	50	51

Val	Cys	Gly	Ser	Ala	Ile
52	53	54	55	56	57

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FIG. 26

KPI(-4-57; I16H, S17W) TW6185

Glu	Val	Val	Arg	Glu	Val	Cys	Ser	Glu	Gln	Ala
-4	-3	-2	-1	1	2	3	4	5	6	7

Glu	Thr	Gly	Pro	Cys	Arg	Ala	Met	His	Trp	Arg
8	9	10	11	12	13	14	15	16	17	18

Trp	Tyr	Phe	Asp	Val	Thr	Glu	Gly	Lys	Cys	Ala
19	20	21	22	23	24	25	26	27	28	29

Pro	Phe	Phe	Tyr	Gly	Gly	Cys	Gly	Gly	Asn	Arg
30	31	32	33	34	35	36	37	38	39	40

Asn	Asn	Phe	Asp	Thr	Glu	Glu	Tyr	Cys	Met	Ala
41	42	43	44	45	46	47	48	49	50	51

Val	Cys	Gly	Ser	Ala	Ile
52	53	54	55	56	57

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Inventor(s): R. Tyler WHITE et. al
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DOCKET NO.: 056324-0129

FIG. 27

KPI(-4-57; M15A, S17F) DD185

Glu	Val	Val	Arg	Glu	Val	Cys	Ser	Glu	Gln	Ala
-4	-3	-2	-1	1	2	3	4	5	6	7

Glu	Thr	Gly	Pro	Cys	Arg	Ala	Ala	Ile	Phe	Arg
8	9	10	11	12	13	14	15	16	17	18

Trp	Tyr	Phe	Asp	Val	Thr	Glu	Gly	Lys	Cys	Ala
19	20	21	22	23	24	25	26	27	28	29

Pro	Phe	Phe	Tyr	Gly	Gly	Cys	Gly	Gly	Asn	Arg
30	31	32	33	34	35	36	37	38	39	40

Asn	Asn	Phe	Asp	Thr	Glu	Glu	Tyr	Cys	Met	Ala
41	42	43	44	45	46	47	48	49	50	51

Val	Cys	Gly	Ser	Ala	Ile
52	53	54	55	56	57

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Title: PROTEASE INHIBITOR PEPTIDES
Inventor(s): R. Tyler WHITE et. al
Serial No. 10/076,604
DOCKET NO.: 056324-0129

FIG. 28

KPI(-4-57; M15A, I16H) TW6173

Glu	Val	Val	Arg	Glu	Val	Cys	Ser	Glu	Gln	Ala
-4	-3	-2	-1	1	2	3	4	5	6	7

Glu	Thr	Gly	Pro	Cys	Arg	Ala	Ala	His	SerTrp	Arg
8	9	10	11	12	13	14	15	16	17	18

Trp	Tyr	Phe	Asp	Val	Thr	Glu	Gly	Lys	Cys	Ala
19	20	21	22	23	24	25	26	27	28	29

Pro	Phe	Phe	Tyr	Gly	Gly	Cys	Gly	Gly	Asn	Arg
30	31	32	33	34	35	36	37	38	39	40

Asn	Asn	Phe	Asp	Thr	Glu	Glu	Tyr	Cys	Met	Ala
41	42	43	44	45	46	47	48	49	50	51

Val	Cys	Gly	Ser	Ala	Ile
52	53	54	55	56	57

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FIG. 29

KPI(-4-57; M15L, I16H) TW6174

Glu	Val	Val	Arg	Glu	Val	Cys	Ser	Glu	Gln	Ala
-4	-3	-2	-1	1	2	3	4	5	6	7

Glu	Thr	Gly	Pro	Cys	Arg	Ala	Leu	His	Ser	Arg
8	9	10	11	12	13	14	15	16	17	18

Trp	Tyr	Phe	Asp	Val	Thr	Glu	Gly	Lys	Cys	Ala
19	20	21	22	23	24	25	26	27	28	29

Pro	Phe	Phe	Tyr	Gly	Gly	Cys	Gly	Gly	Asn	Arg
30	31	32	33	34	35	36	37	38	39	40

Asn	Asn	Phe	Asp	Thr	Glu	Glu	Tyr	Cys	Met	Ala
41	42	43	44	45	46	47	48	49	50	51

Val	Cys	Gly	Ser	Ala	Ile
52	53	54	55	56	57

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FIG. 30

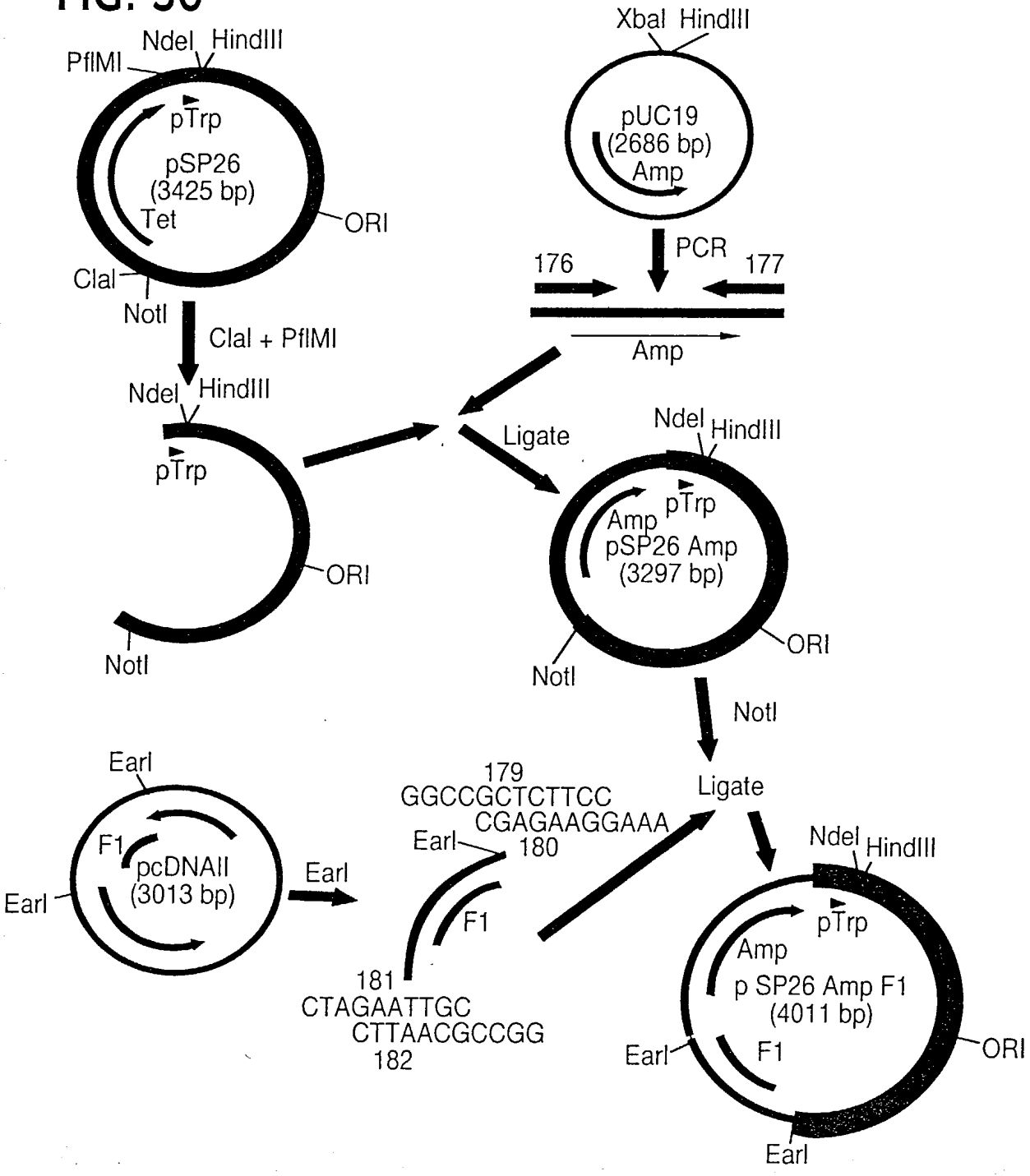

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FIG. 31

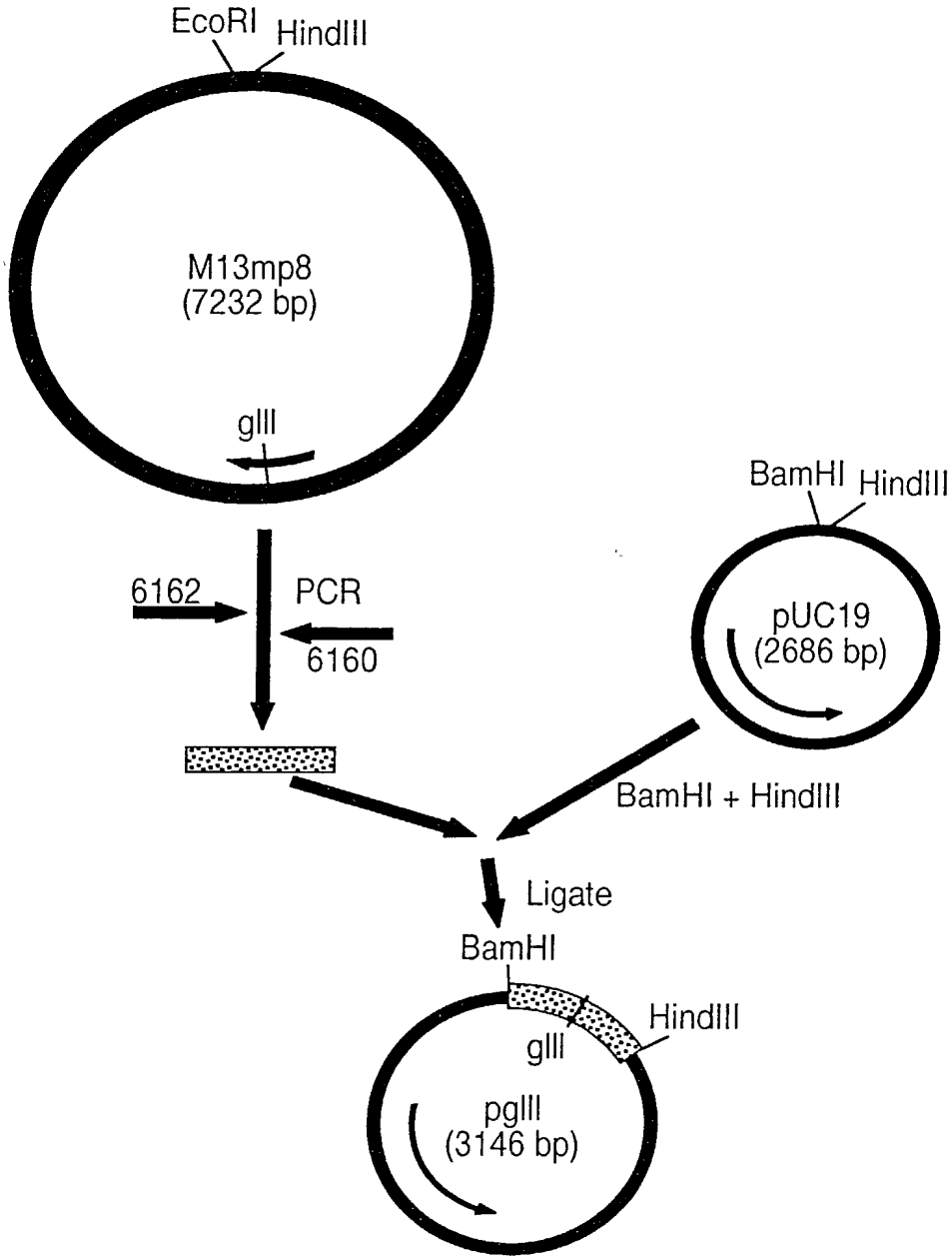

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FIG. 32

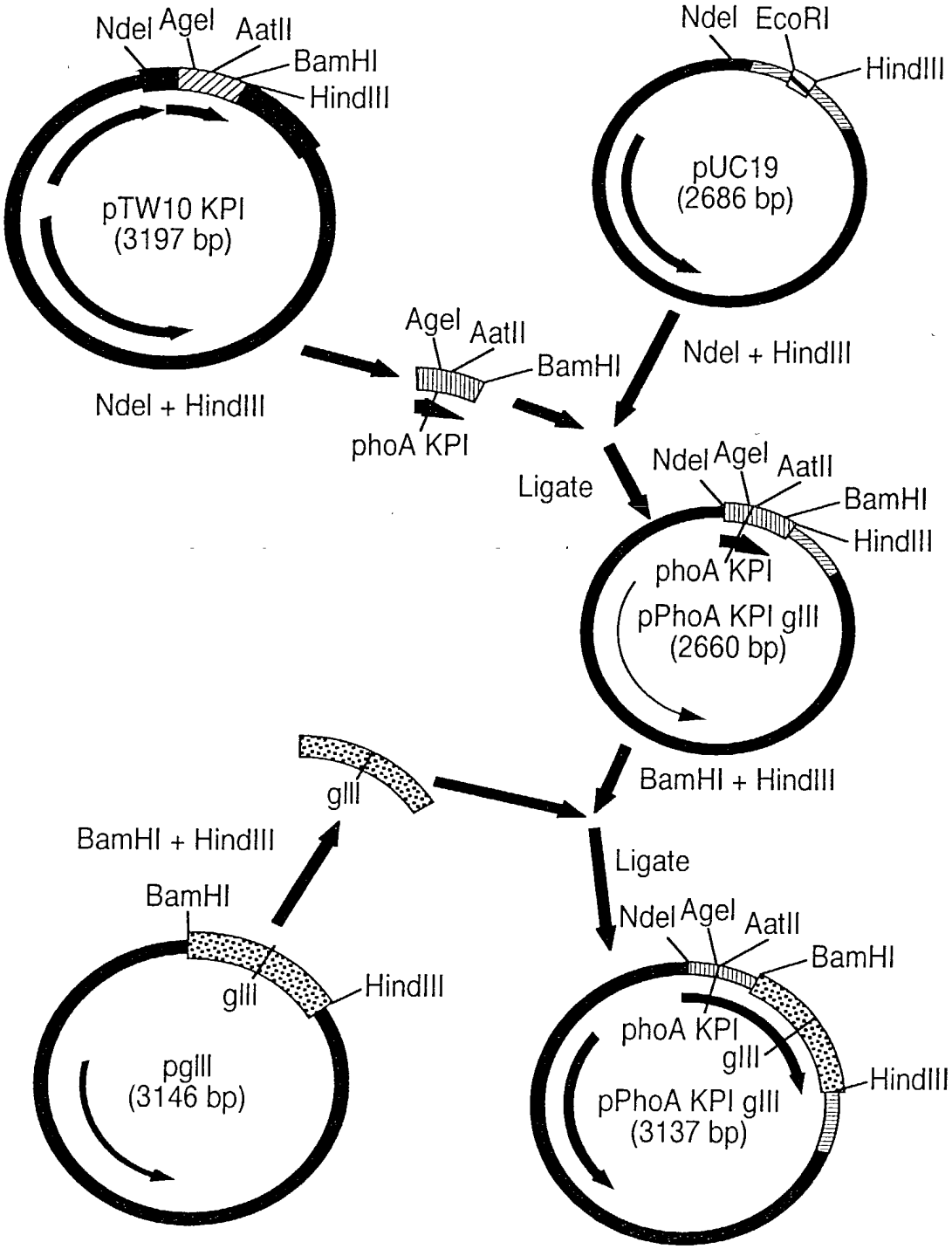

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FIG. 33

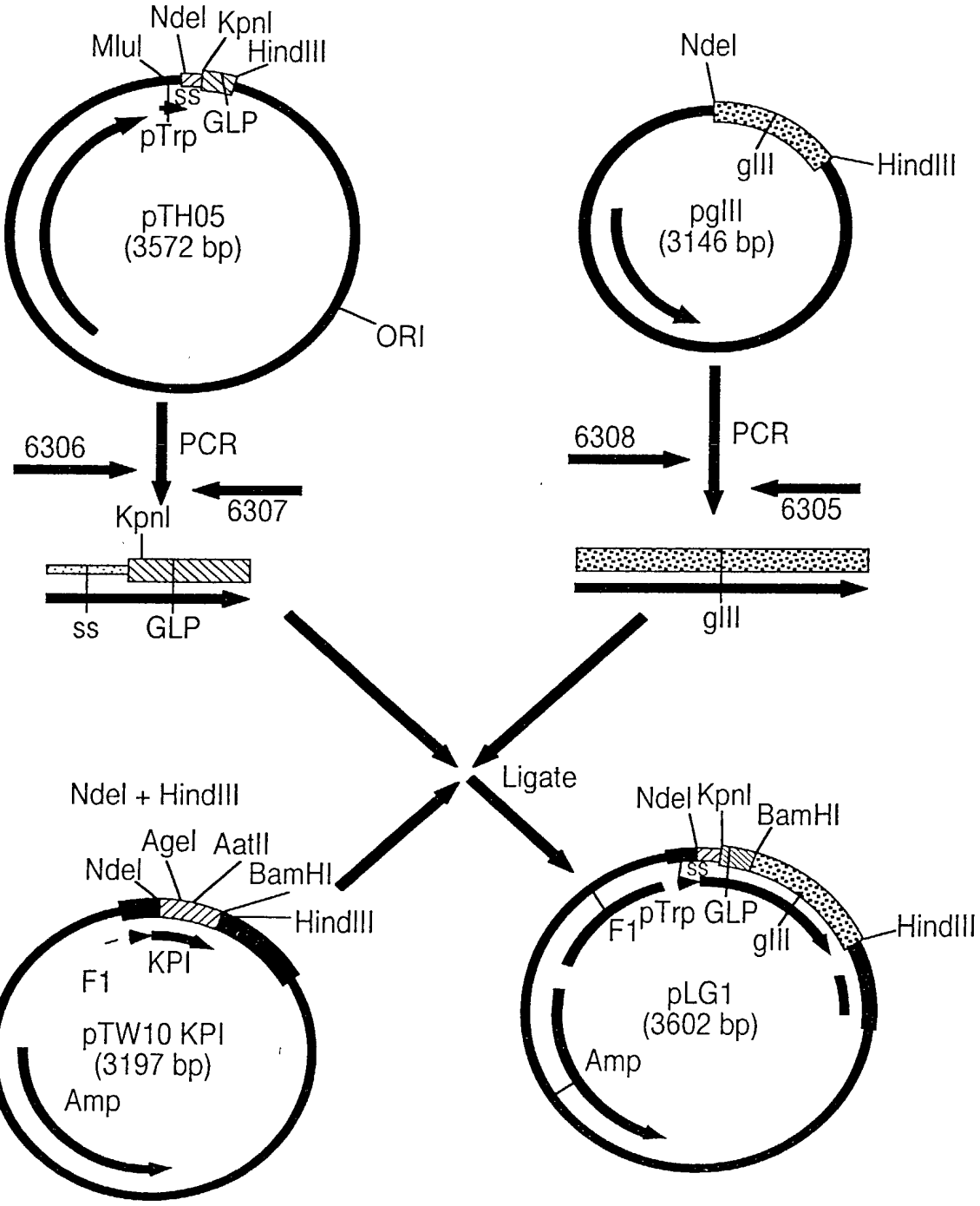

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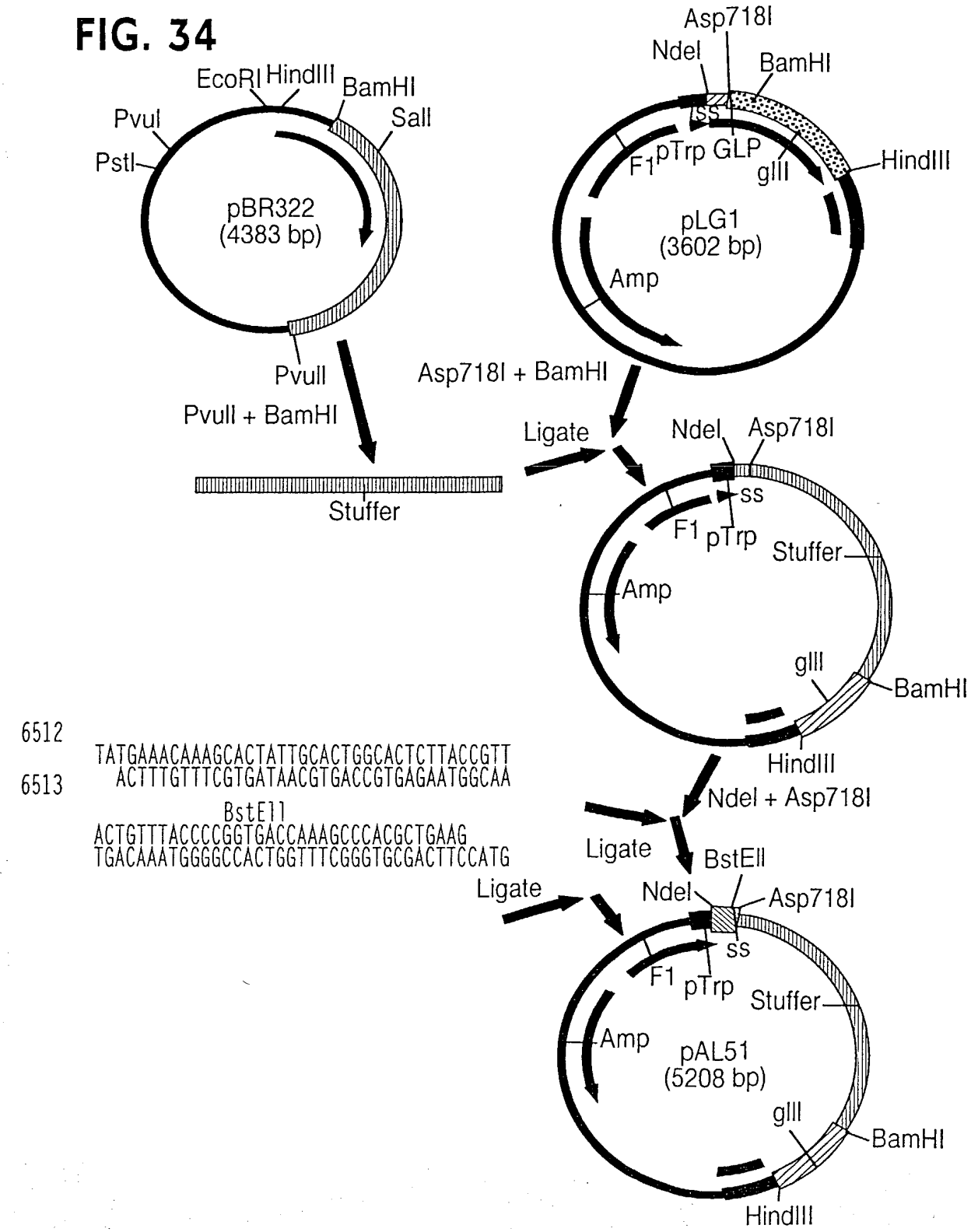
FIG. 34



6512 TATGAAACAAAGCACTATTGCACTGGCACTCTTACCGTT
6513 ACTTTGTTTCGTGATAACGTGACCGTGAGAATGGCAA

BstEII
ACTGTTTACCCCGGTGACCAAAGCCCACGCTGAAG
TGACAAATGGGGCCACTGGTTTCGGGTGCGACTTCCATG

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FIG. 35

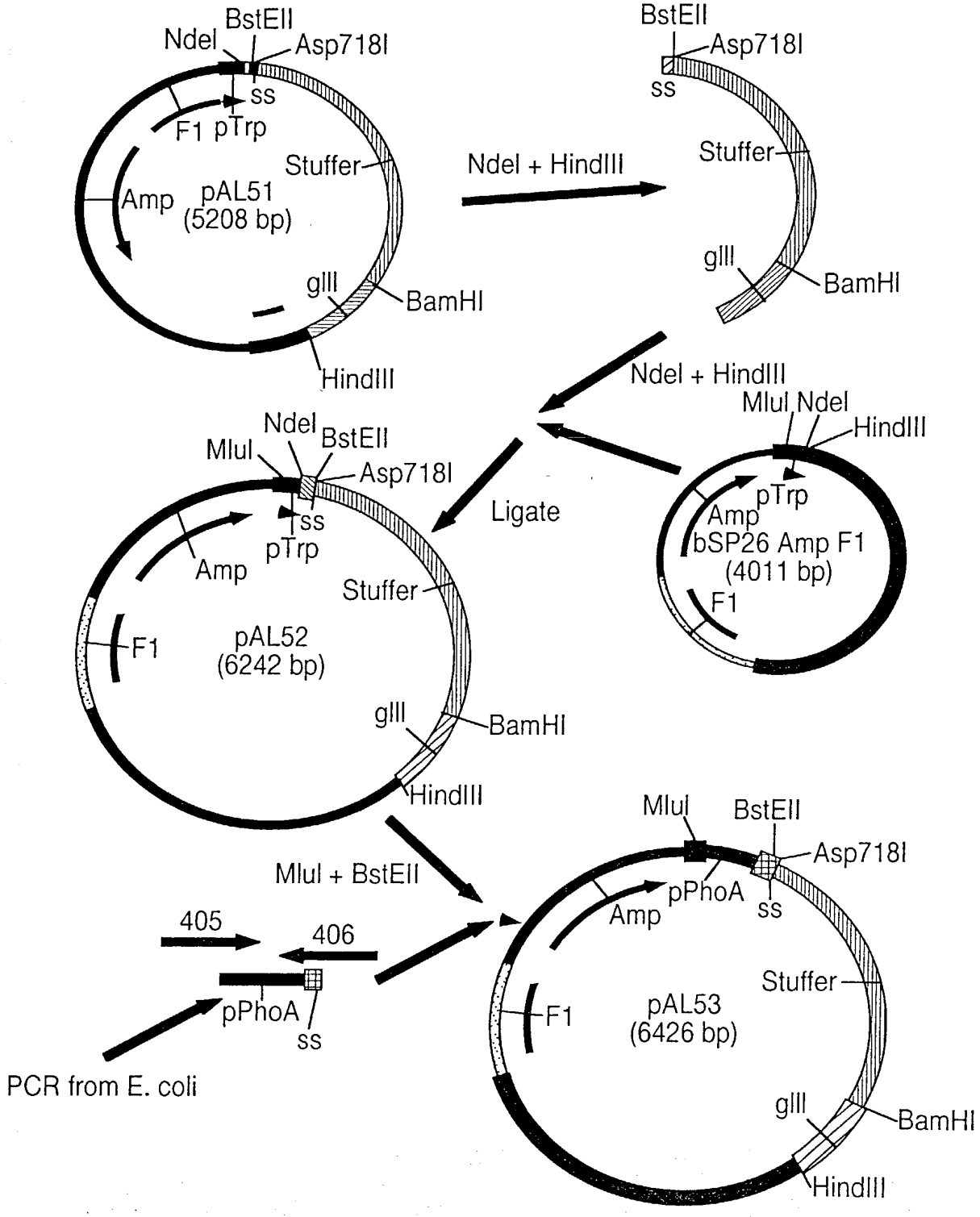

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FIG. 36

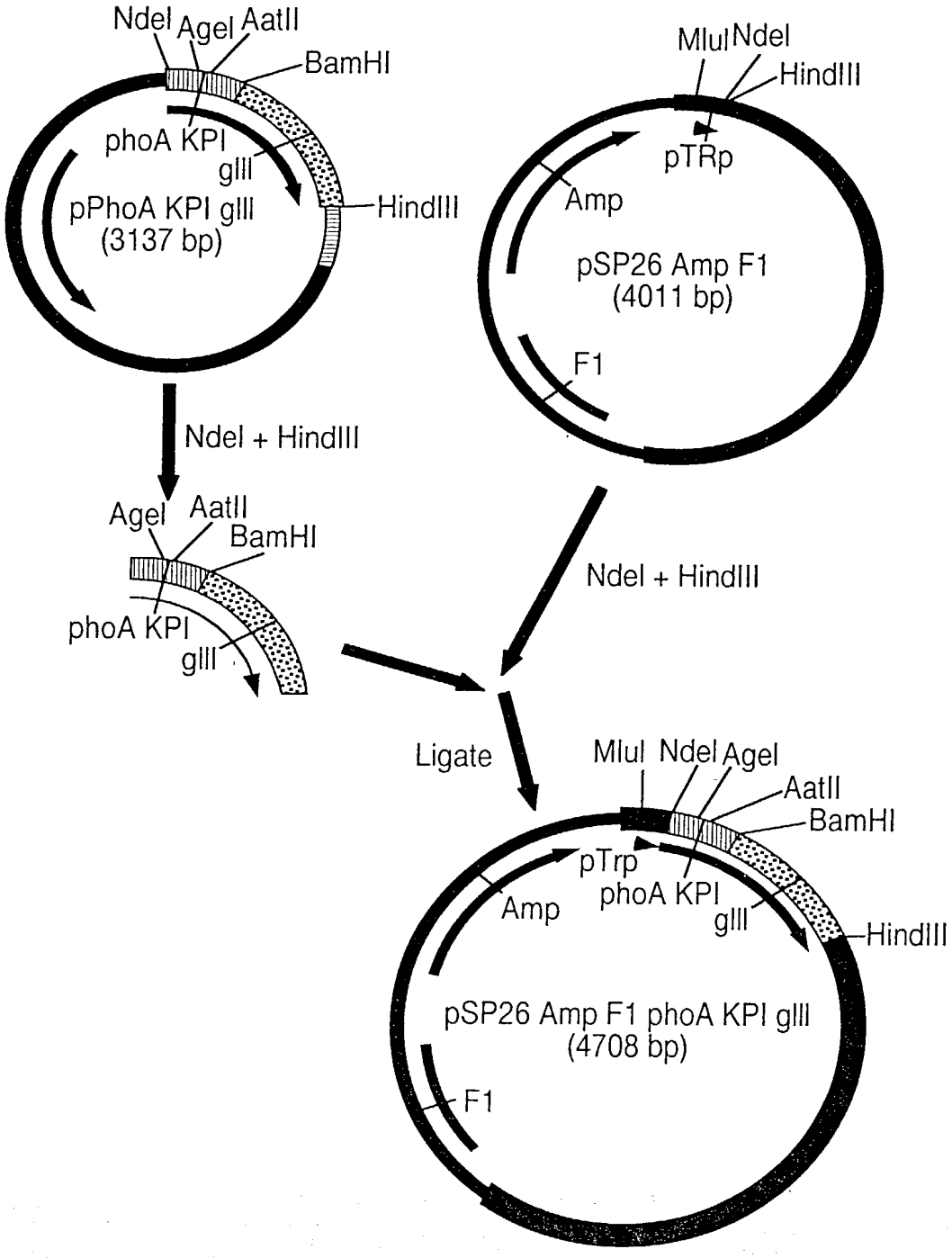

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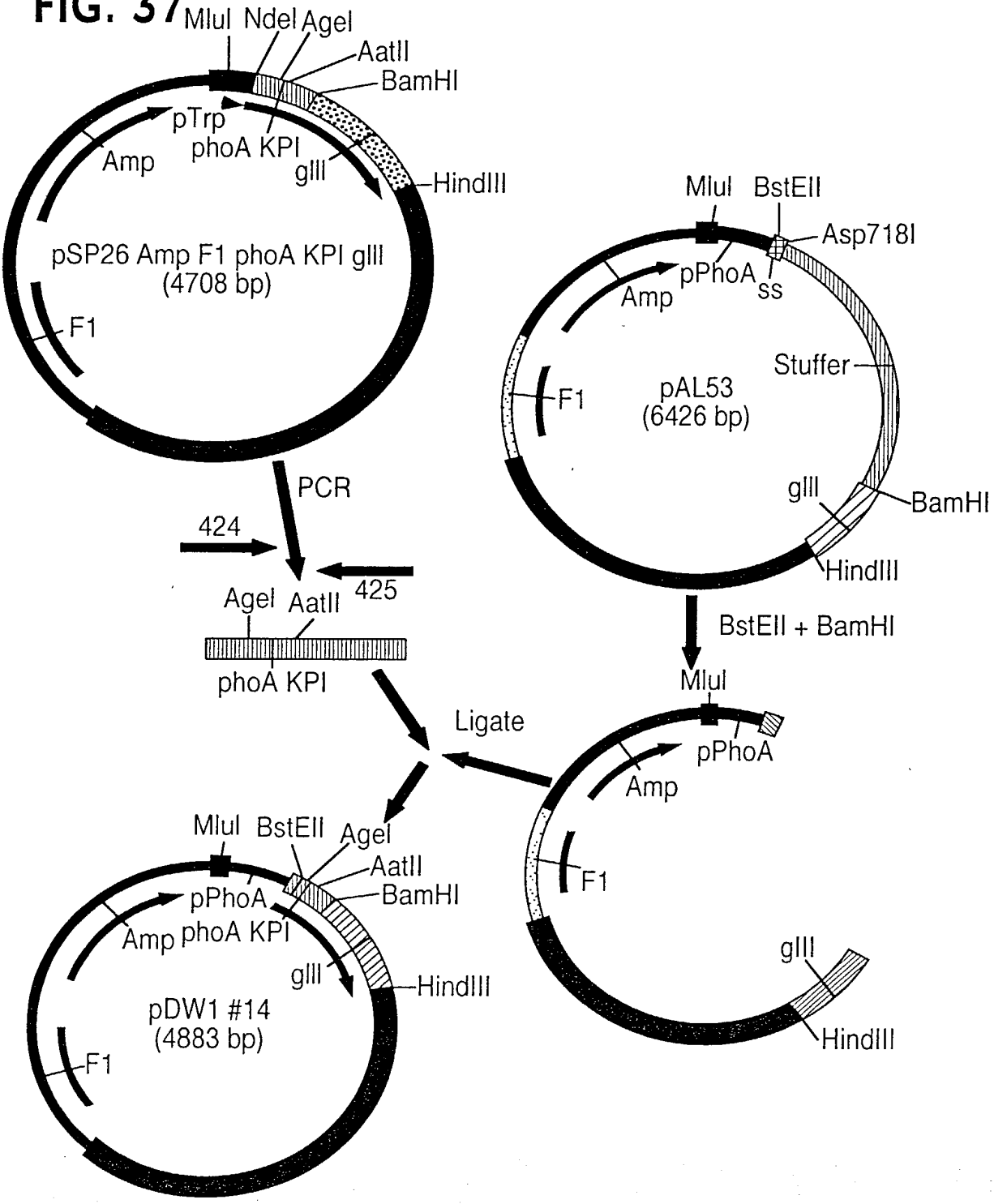
FIG. 37



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Inventor(s): R. Tyler WHITE et. al
Serial No. 10/076,604
DOCKET NO.: 056324-0129

FIG. 38

phoA signal →

BstEII

GTG AAA CAA AGC ACT ATT GCA CTG GCA CTC TTA CCG TTA CTG TTT ACC CCG GTG ACC AAA
Val Lys Gln Ser Thr Ile Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr Pro Val Thr Lys

KPI (1-55) →

AgeI

GCC GAG GTG TGC TCT GAA CAA GCT GAG ACC GGT CCG TGC CGT GCA ATG ATC TCC CGC TGG
Ala Glu Val Cys Ser Glu Gln Ala Glu Thr Gly Pro Cys Arg Ala Met Ile Ser Arg Trp

AatII

TAC TTT GAC GTC ACT GAA GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC
Tyr Phe Asp Val Thr Glu Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn

BamHI gIII →

CGT AAC AAC TTT GAC ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GGT GGT GGC TCT
Arg Asn Asn Phe Asp Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Gly Gly Gly Ser

GGT TCC GGT GAT TTT GAT TAT GAA AAG ATG GCA AAC GCT AAT AAG GGG GCT ATG ACC GAA
Gly Ser Gly Asp Phe Asp Tyr Glu Lys Met Ala Asn Ala Asn Lys Gly Ala Met Thr Glu

AAT GCC GAT GAA AAC GCG CTA CAG TCT GAC GCT AAA GGC AAA CTT GAT TCT GTC GCT ACT
Asn Ala Asp Glu Asn Ala Leu Gln Ser Asp Ala Lys Gly Lys Leu Asp Ser Val Ala Thr

GAT TAC GGT GCT GCT ATC GAT GGT TTC ATT GGT GAC GTT TCC GGC CTT GCT AAT GGT AAT
Asp Tyr Gly Ala Ala Ile Asp Gly Phe Ile Gly Asp Val Ser Gly Leu Ala Asn Gly Asn

GGT GCT ACT GGT GAT TTT GCT GGC TCT AAT TCC CAA ATG GCT CAA GTC GGT GAC GGT GAT
Gly Ala Thr Gly Asp Phe Ala Gly Ser Asn Ser Gln Met Ala Gln Val Gly Asp Gly Asp

AAT TCA CCT TTA ATG AAT AAT TTC CGT CAA TAT TTA CCT TCC CTC CCT CAA TCG GTT GAA
Asn Ser Pro Leu Met Asn Asn Phe Arg Gln Tyr Leu Pro Ser Leu Pro Gln Ser Val Glu

TGT CGC CCT TTT GTC TTT GGC GCT GGT AAA CCA TAC GAA TTT TCT ATT GAT TGT GAC AAA
Cys Arg Pro Phe Val Phe Gly Ala Gly Lys Pro Tyr Glu Phe Ser Ile Asp Cys Asp Lys

ATA AAC TTA TTC CGT GGT GTC TTT GCG TTT CTT TTA TAT GTT GCC ACC TTT ATG TAT GTA
Ile Asn Leu Phe Arg Gly Val Phe Ala Phe Leu Leu Tyr Val Ala Thr Phe Met Tyr Val

TTT TCT ACG TTT GCT AAC ATA CTG CGT AAT AAG GAG TCT TAA TA
Phe Ser Thr Phe Ala Asn Ile Leu Arg Asn Lys Glu Ser • ••

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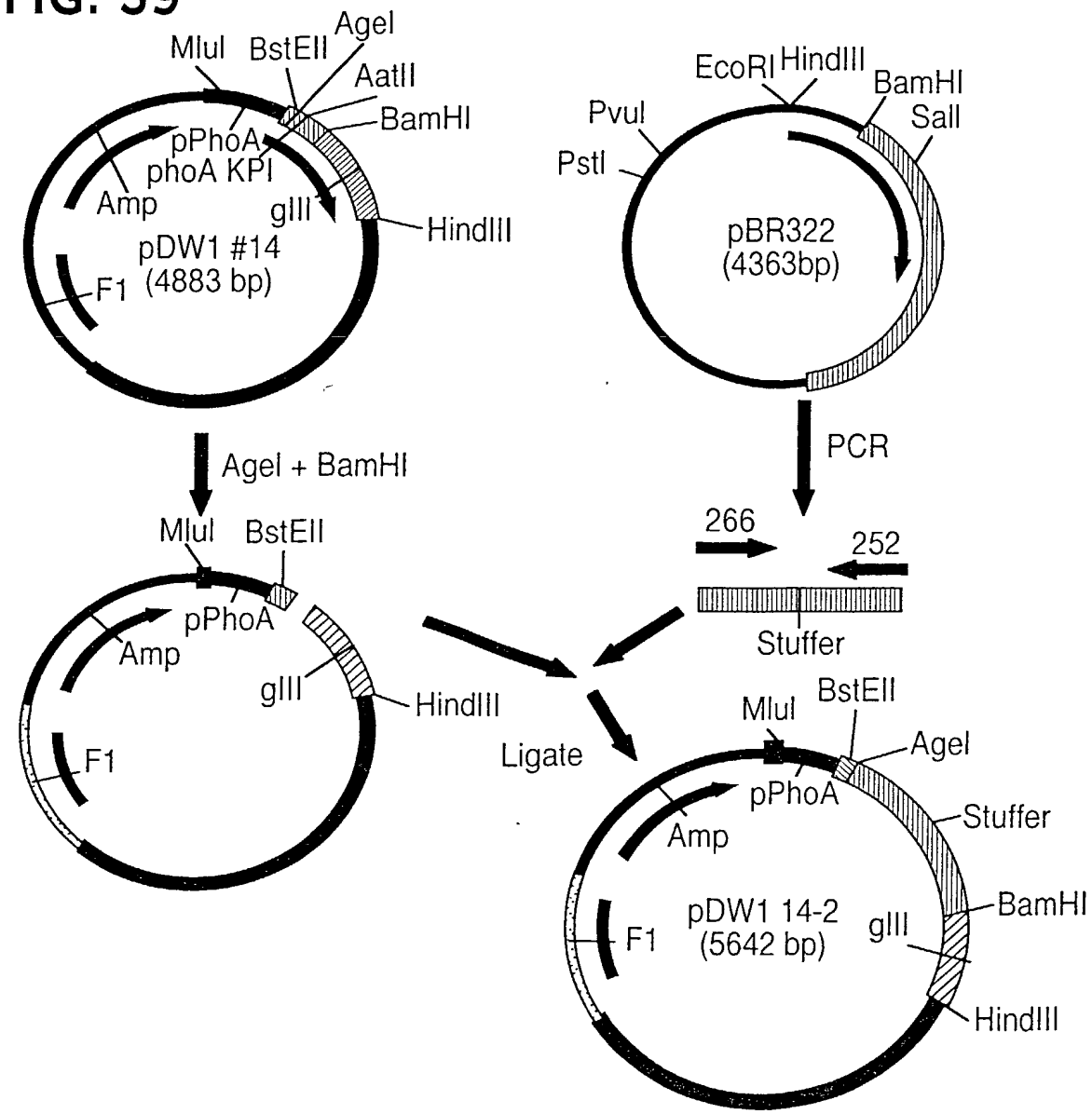
FIG. 39



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Inventor(s): R. Tyler WHITE et. al
Serial No. 10/076,604
DOCKET NO.: 056324-0129

FIG. 40

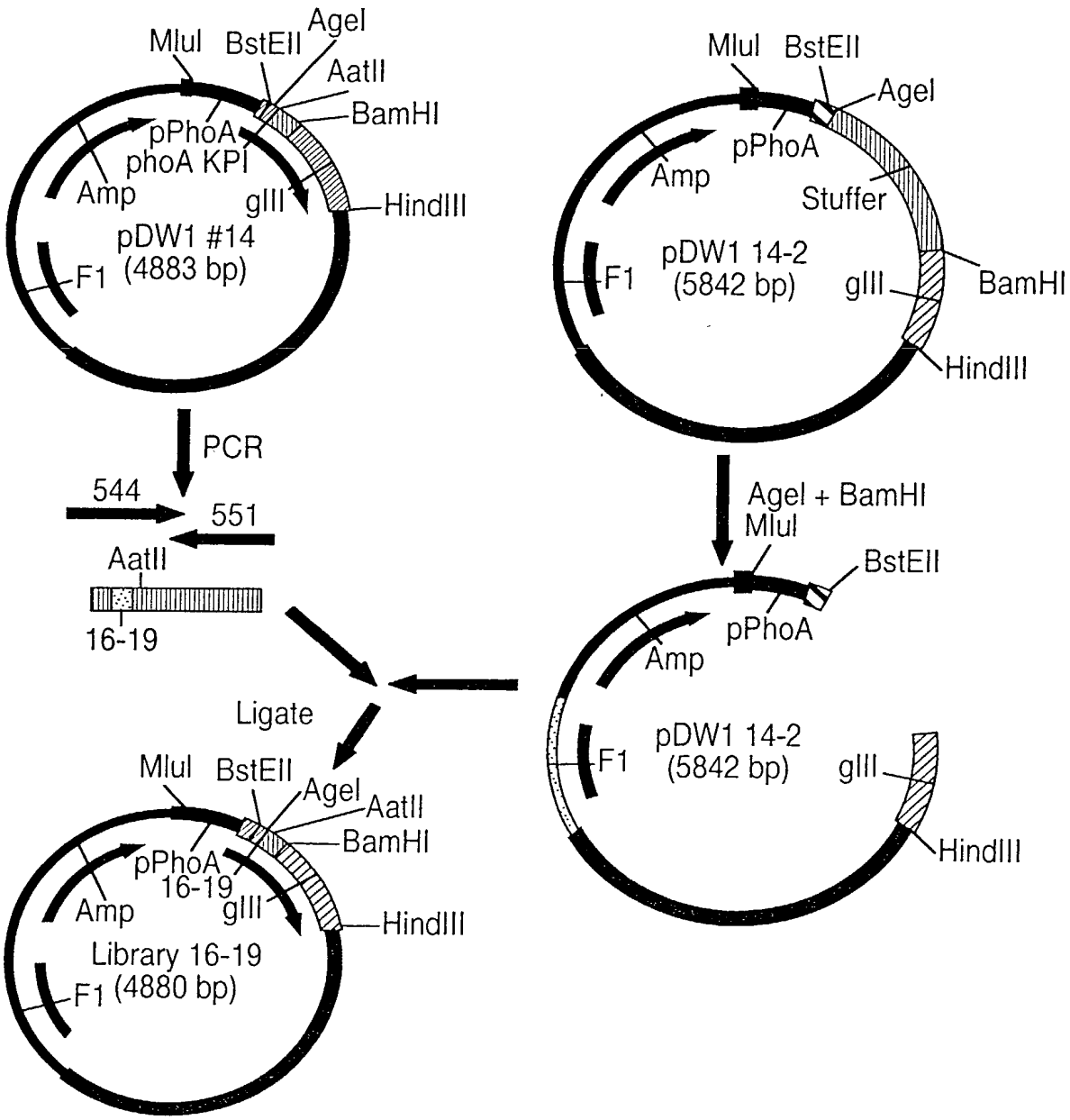

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FIG. 41

phoA signal →

BstEII

GTG AAA CAA AGC ACT ATT GCA CTG GCA CTC TTA CCG TTA CTG TTT ACC CCG GTG ACC AAA
Val Lys Gln Ser Thr Ile Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr Pro Val Thr Lys

KPI (1-55; 16 - 19) → AgeI 16 - 19

GCC GAG GTG TGC TCT GAA CAA GCT GAG ACC GGT CCG TGC CGT NNS NNS NNS NNS TGG TAC
Ala Glu Val Cys Ser Glu Gln Ala Glu Thr Gly Pro Cys Arg --- --- --- --- Trp Tyr

AatII

TTT GAC GTC ACT GAA GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT
Phe Asp Val Thr Glu Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg

BamHI gIII →

AAC AAC TTT GAC ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GGT GGT GGC TCT GGT
Asn Asn Phe Asp Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Gly Gly Gly Ser Gly

TCC GGT GAT TTT GAT TAT GAA AAG ATG GCA AAC GCT AAT AAG GGG GCT ATG ACC GAA AAT
Ser Gly Asp Phe Asp Tyr Glu Lys Met Ala Asn Ala Asn Lys Gly Ala Met Thr Glu Asn

GCC GAT GAA AAC GCG CTA CAG TCT GAC GCT AAA GGC AAA CTT GAT TCT GTC GCT ACT GAT
Ala Asp Glu Asn Ala Leu Gln Ser Asp Ala Lys Gly Lys Leu Asp Ser Val Ala Thr Asp

TAC GGT GCT GCT ATC GAT GGT TTC ATT GGT GAC GTT TCC GGC CTT GCT AAT GGT AAT GGT
Tyr Gly Ala Ala Ile Asp Gly Phe Ile Gly Asp Val Ser Gly Leu Ala Asn Gly Asn Gly

gIII

GCT ACT GGT GAT TTT GCT GGC TCT AAT TCC CAA ATG GCT CAA GTC GGT GAC GGT GAT AAT
Ala Thr Gly Asp Phe Ala Gly Ser Asn Ser Gln Met Ala Gln Val Gly Asp Gly Asp Asn

TCA CCT TTA ATG AAT AAT TTC CGT CAA TAT TTA CCT TCC CTC CCT CAA TCG GTT GAA TGT
Ser Pro Leu Met Asn Asn Phe Arg Gln Tyr Leu Pro Ser Leu Pro Gln Ser Val Glu Cys

CGC CCT TTT GTC TTT GGC GCT GGT AAA CCA TAC GAA TTT TCT ATT GAT TGT GAC AAA ATA
Arg Pro Phe Val Phe Gly Ala Gly Lys Pro Tyr Glu Phe Ser Ile Asp Cys Asp Lys Ile

AAC TTA TTC CGT GGT GTC TTT GCG TTT CTT TTA TAT GTT GCC ACC TTT ATG TAT GTA TTT
Asn Leu Phe Arg Gly Val Phe Ala Phe Leu Leu Tyr Val Ala Thr Phe Met Tyr Val Phe

TCT ACG TTT GCT AAC ATA CTG CGT AAT AAG GAG TCT TAA TA
Ser Thr Phe Ala Asn Ile Leu Arg Asn Lys Glu Ser • ••

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FIG. 42

phoA signal →

BstEII

GTG AAA CAA AGC ACT ATT GCA CTG GCA CTC TTA CCG TTA CTG TTT ACC CCG GTG ACC AAA
Val Lys Gln Ser Thr Ile Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr Pro Val Thr Lys

KPI (1-55; M15A, S17F) →

AgeI

GCC GAG GTG TGC TCT GAA CAA GCT GAG ACC GGT CCG TGC CGT GCA GCT ATC TTC CGC TGG
Ala Glu Val Cys Ser Glu Gln Ala Glu Thr Gly Pro Cys Arg Ala Ala Ile Phe Arg Trp

AatII

TAC TTT GAC GTC ACT GAA GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC
Tyr Phe Asp Val Thr Glu Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn

BamHI gIII →

CGT AAC AAC TTT GAC ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GGT GGT GGC TCT
Arg Asn Asn Phe Asp Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Gly Gly Gly Ser

GGT TCC GGT GAT TTT GAT TAT GAA AAG ATG GCA AAC GCT AAT AAG GGG GCT ATG ACC GAA
Gly Ser Gly Asp Phe Asp Tyr Glu Lys Met Ala Asn Ala Asn Lys Gly Ala Met Thr Glu

AAT GCC GAT GAA AAC GCG CTA CAG TCT GAC GCT AAA GGC AAA CTT GAT TCT GTC GCT ACT
Asn Ala Asp Glu Asn Ala Leu Gln Ser Asp Ala Lys Gly Lys Leu Asp Ser Val Ala Thr

GAT TAC GGT GCT GCT ATC GAT GGT TTC ATT GGT GAC GTT TCC GGC CTT GCT AAT GGT AAT
Asp Tyr Gly Ala Ala Ile Asp Gly Phe Ile Gly Asp Val Ser Gly Leu Ala Asn Gly Asn

GGT GCT ACT GGT GAT TTT GCT GGC TCT AAT TCC CAA ATG GCT CAA GTC GGT GAC GGT GAT
Gly Ala Thr Gly Asp Phe Ala Gly Ser Asn Ser Gln Met Ala Gln Val Gly Asp Gly Asp

AAT TCA CCT TTA ATG AAT AAT TTC CGT CAA TAT TTA CCT TCC CTC CCT CAA TCG GTT GAA
Asn Ser Pro Leu Met Asn Asn Phe Arg Gln Tyr Leu Pro Ser Leu Pro Gln Ser Val Glu

TGT CGC CCT TTT GTC TTT GGC GCT GGT AAA CCA TAC GAA TTT TCT ATT GAT TGT GAC AAA
Cys Arg Pro Phe Val Phe Gly Ala Gly Lys Pro Tyr Glu Phe Ser Ile Asp Cys Asp Lys

ATA AAC TTA TTC CGT GGT GTC TTT GCG TTT CTT TTA TAT GTT GCC ACC TTT ATG TAT GTA
Ile Asn Leu Phe Arg Gly Val Phe Ala Phe Leu Leu Tyr Val Ala Thr Phe Met Tyr Val

TTT TCT ACG TTT GCT AAC ATA CTG CGT AAT AAG GAG TCT TAA TA
Phe Ser Thr Phe Ala Asn Ile Leu Arg Asn Lys Glu Ser

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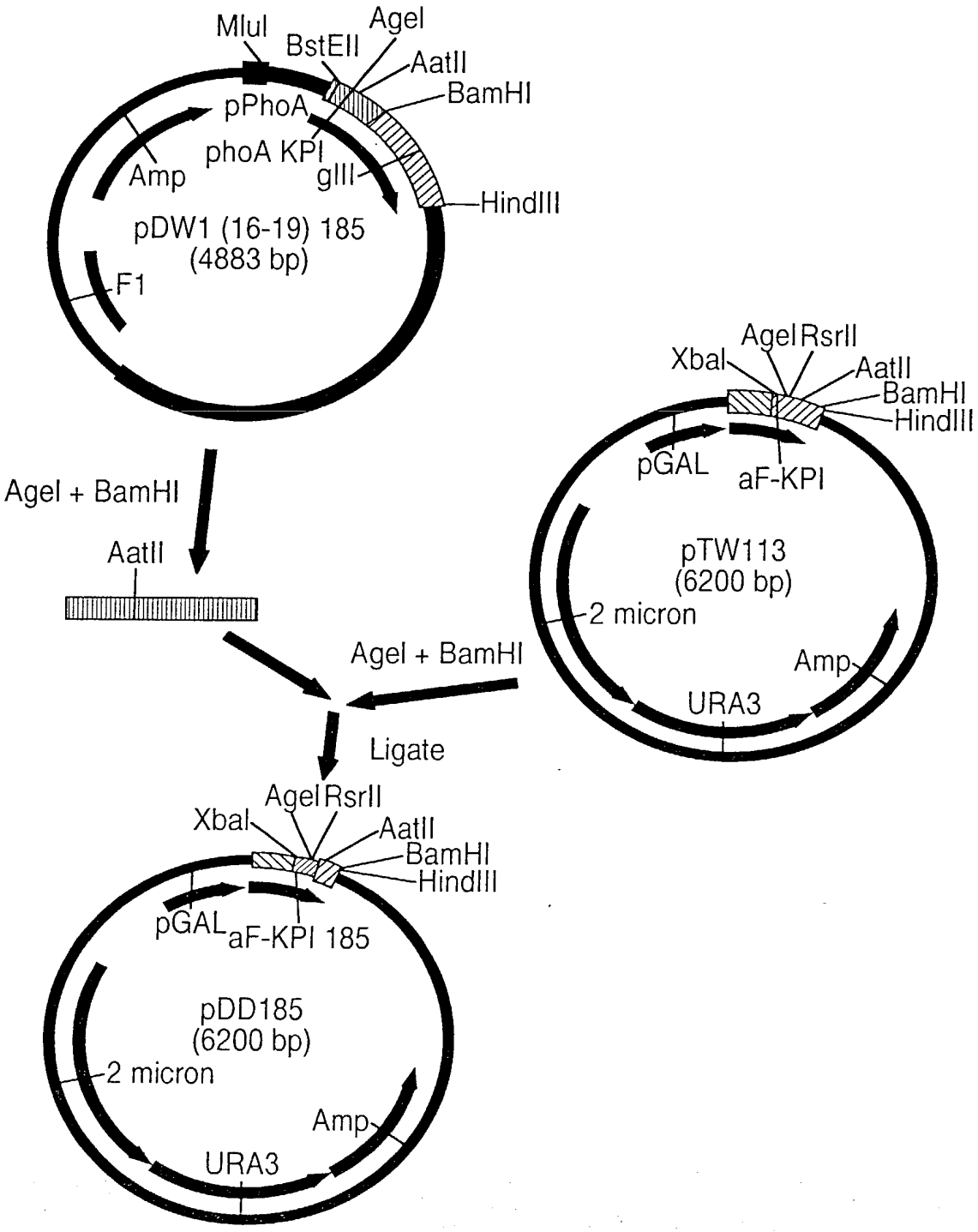
FIG. 43



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Inventor(s): R. Tyler WHITE et. al
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DOCKET NO.: 056324-0129

pDD185

FIG. 44

α-factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT
TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA
Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC
CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG
Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG
Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT
Ser Thr Asn Asn Gly Leu Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys

XbaI

KPI(-4-57; M15A, S17F)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA
CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT
Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

RsrII

AgeI

AatII

GCT GAG ACC GGT CCG TGC CGT GCA GCT ATC TTC CGC TGG TAC TTT GAC GTC ACT GAA
CGA CTC TGG CCA GGC ACG GCA CGT CGA TAG AAG GCG ACC ATG AAA CTG CAG TGA CTT
Ala Glu Thr Gly Pro Cys Arg Ala Ala Ile Phe Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC
CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG
Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A
Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala Ile

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FIG. 45

Plasma kallikrein inhibition by KPI (-4-57) variants

Variant		Substitution			K_i(nM)
		15	16	17	
TW113	KPI (-4-57)				45.00
DD185	KPI (-4-57; M15A, S17F)	A		F	0.39
TW6165	KPI (-4-57; M15A, S17W)	A		W	0.65
TW6166	KPI (-4-57; M15A, S17Y)	A		Y	0.40
TW6175	KPI (-4-57; M15L, S17F)	L		F	0.50
BG028	KPI (-4-57; M15L, S17Y)	L		Y	1.10
TW6183	KPI (-4-57; I16H, S17F)		H	F	1.20
TW6184	KPI (-4-57; I16H, S17Y)		H	Y	0.91
TW6185	KPI (-4-57; I16H, S17W)		H	W	1.30
TW6173	KPI (-4-57; M15A, I16H)	A	H		1.00
TW6174	KPI (-4-57; M15L, I16H)	L	H		0.90

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FIG. 46A

Variant	Sequence	Inhibition Ki (nM)			
		kallikrei	Plasmin	XIIa	Xa
Aprotinin	RPDFCLEPPYTGPCKARIIRYFYNAKAGLCQTFVYGGCRAKRNNFKSAEDCMRTCGGA	20.00	0.23	5000.0	
Aprotinin R15, S42	DFCLEPPYTGPCRARIIRYFYNAKAGLCQTFVYGGCRAKSNNFKSAEDCMRTCGGA	0.91	0.17	3983.0	
KPI (-4-57)	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	45.00	34.00	3718.0	161.0
TW6167	EVVREVCSEQAEPGPCRAMISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	61.00		3641.0	288.0
BG031	EVVREVCSEQAEVGPCRAMISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	34.00		498.0	
BG032	EVVREVCSEQAESGPCRAMISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	49.00		731.0	
TW101	EVCSEQAETGPCKAMISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	2000.00	11.50		
TW6208	EVVREVCSEQAETGPCRGMISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI			369.0	
TW106	EVCSEQAETGPCRARISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	560.00	3.70		
DD108	EVVREVCSEQAETGPCRAAISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	1.70	11.20	1600.0	123.0
DD109	EVVREVCSEQAETGPCRAIISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	9.50		1681.0	421.0
DD110	EVVREVCSEQAETGPCRALISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	2.10		624.0	55.0
DD111	EVVREVCSEQAETGPCRASISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	5.60			
DD112	EVVREVCSEQAETGPCRAVISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	6.80		998.0	
TW6179	EVVREVCSEQAETGPCRAGISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	78.00		368.0	

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FIG. 46B

TW6163	EVVREVCSEQAETGPCRAMHSRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	4.70	103.58	4532.0	457.0
TW6172	EVVREVCSEQAETGPCRAMASRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	315.00			1463.0
TW6180	EVVREVCSEQAETGPCRAMFSRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	70.00		885.0	39.0
TW6181	EVVREVCSEQAETGPCRAMKSRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	150.00		1514.0	
BG001	EVVREVCSEQAETGPCRAMLSRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	38.00	10.00	489.0	204.0
TW116	EVCSEQAETGPCRAMIIRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	145.00	89.00		806.0
DD102	EVVREVCSEQAETGPCRAMIPRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	16.00		315.0	
DD103	EVVREVCSEQAETGPCRAMIFRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	17.00		2128.0	110.0
DD104	EVVREVCSEQAETGPCRAMIYRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	15.00		237.0	345.0
DD105	EVVREVCSEQAETGPCRAMIWRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	18.00		198.0	320.0
TW6168	EVVREVCSEQAETGPCRAMILRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	25.80		3521.0	395.0
TW6182	EVVREVCSEQAETGPCRAMIHRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	36.00		752.0	
TW6194	EVVREVCSEQAETGPCRAMIERWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	70.83			
TW6210	EVVREVCSEQAETGPCRAMIQRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	54.00		277.0	
CL006	EVVREVCSEQAETGPCRAMISAWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	110.20		89600.0	133.0
BG012	EVVREVCSEQAETGPCRAMISTWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI			40.0	116.0

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FIG. 46C

TW6209	EVVREVCSEQAETGPCRAMISHWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	81.00	45.90	184.0	613.0
TW6211	EVVREVCSEQAETGPCRAMISKWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	184.00		402.0	
DD128	EVVREVCSEQAETGPCRAMISLWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	44.00			37.0
TW6142	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFVYGGCGGNRNNFDTEEYCMAVCGSAI	18.00	18.00	7972.0	225.0
AL301	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFLYGGCGGNRNNFDTEEYCMAVCGSAI	216.00		1557.0	
AL302	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFGYGGCGGNRNNFDTEEYCMAVCGSAI	39.00			316.0
TW6147	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCAGNRNNFDTEEYCMAVCGSAI	35.00		1090.0	179.0
TW6138	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCKGNRNNFDTEEYCMAVCGSAI	18.00		921.0	309.0
TW6154	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCLGNRNNFDTEEYCMAVCGSAI	11.00		915.0	39.0
TW6155	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCMGNRNNFDTEEYCMAVCGSAI	11.00			27.0
TW6140	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCNGNRNNFDTEEYCMAVCGSAI	35.00		475.0	
TW6156	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCPGNRNNFDTEEYCMAVCGSAI				
TW6141	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCQGNRNNFDTEEYCMAVCGSAI	42.00			
TW118	EVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCRGNRNNFDTEEYCMAVCGSAI	6.00	24.00	13009.0	68.0
DD100	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCCGNRNNFDTEEYCMAVCGSAI	15.00			
TW6157	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCSGNRNNFDTEEYCMAVCGSAI	40.00		511.0	168.0
TW6158	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCTGNRNNFDTEEYCMAVCGSAI	29.00			

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FIG. 46D

TW6159	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCVGNRNNFDTEEYCMAVCGSAI	17.00			64.0
TW6161	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCYGNRNNFDTEEYCMAVCGSAI	7.50	18.00	1507.0	8.7
DD101	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCDGNRNNFDTEEYCMAVCGSAI	64.00		924.0	
TW6151	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCEGNRNNFDTEEYCMAVCGSAI	163.00		1162.0	954.0
TW6139	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCHGNRNNFDTEEYCMAVCGSAI	19.00	22.80	152.0	78.0
TW6153	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCIGNRNNFDTEEYCMAVCGSAI	11.20	21.30	65.0	36.0
TW122	EVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCGANRNNFDTEEYCMAVCGSAI	32.00	27.00		581.0
TW6178	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCGRNRNNFDTEEYCMAVCGSAI	16.00		444.0	
TW6148	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCGGARNNFDTEEYCMAVCGSAI	40.00			
TW124	EVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCGGNSNNFDTEEYCMAVCGSAI	64.00	48.00		
TW6149	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCGGNANNFDTEEYCMAVCGSAI	54.00			
TW6173	EVVREVCSEQAETGPCRAAHSRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	1.00	7.24	1432.0	
TW6174	EVVREVCSEQAETGPCRALHSRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	0.90	6.89	2796.0	
BG002	EVVREVCSEQAETGPCRALLSRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	0.98	19.00	403.0	60.0
DD129	EVVREVCSEQAETGPCRALFSRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	3.60		1864.0	6.0
DD185	EVVREVCSEQAETGPCRAAIFRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	0.39	8.71	150.0	196.0

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FIG. 46E

TW6165	EVVREVCSEQAETGPCRAAIWRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	0.65	16.40	206.0	
TW6166	EVVREVCSEQAETGPCRAAIYRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	0.4	10.10	73.0	
BG028	EVVREVCSEQAETGPCRALIYRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	1.10	12.10	93.8	
TW6169	EVVREVCSEQAETGPCRALILRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	1.20		619.0	111.0
DD113	EVVREVCSEQAETGPCRALIPRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	0.85	12.80	293.0	74.0
TW6175	EVVREVCSEQAETGPCRALIFRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	0.50	7.46	35.0	56.0
TW6201	EVVREVCSEQAETGPCRAGIYRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	34.60		419.0	
TW6202	EVVREVCSEQAETGPCRAGIWRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	128.50		1237.0	
TW6203	EVVREVCSEQAETGPCRAGIPRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	31.20		5045.0	
TW6204	EVVREVCSEQAETGPCRAAISAWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI			147.0	87.0
TW6205	EVVREVCSEQAETGPCRALISAWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI			195.0	29.0
DD114	EVVREVCSEQAETGPCRAAISRWYFDVTEGKCAPFFYGGCRGNRNNFDTEEYCMAVCGSAI	0.70	7.77	224.0	
TW6190	EVVREVCSEQAETGPCRAAISRWYFDVTEGKCAPFFYGGCYGNRNNFDTEEYCMAVCGSAI	0.83	52.20	589.0	1396.0
TW6183	EVVREVCSEQAETGPCRAMHFRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	1.20	11.68	12440.0	159.0
TW6184	EVVREVCSEQAETGPCRAMHYRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	0.91	11.96	14000.0	214.0
TW6185	EVVREVCSEQAETGPCRAMHWRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	1.30	18.60	388.0	473.0
BG003	EVVREVCSEQAETGPCRAMLHRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	36.00		467.0	

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FIG. 46F

TW6186	EVVREVCSEQAETGPCRAMHSRWYFDVTEGKCAPFFYGGCYGNRNNFDTEEYCMAVCGSAI	0.48	8.86	186.0	11.0
TW6187	EVVREVCSEQAETGPCRAMIFRWYFDVTEGKCAPFFYGGCYGNRNNFDTEEYCMAVCGSAI	3.80	15.40	92.0	15.0
TW6188	EVVREVCSEQAETGPCRAMIYRWYFDVTEGKCAPFFYGGCYGNRNNFDTEEYCMAVCGSAI	4.00		419.0	24.0
TW6189	EVVREVCSEQAETGPCRAMIWRWYFDVTEGKCAPFFYGGCYGNRNNFDTEEYCMAVCGSAI	4.00			34.0
TW6170	EVVREVCSEQAEPGPCRALILRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	2.50			452.0
DD115	EVVREVCSEQAETGPCRGYITRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI			213.0	299.0
DD170	EVVREVCSEQAETGPCRALHNRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	0.99	18.00	550.0	
TW6176	EVVREVCSEQAETGPCRAAHFRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	3.50	118.00	56.0	
TW6177	EVVREVCSEQAETGPCRALHFRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	7.20	32.70	245.0	156.0
BG006	EVVREVCSEQAETGPCRAALFRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	0.30	12.10	80.0	
DD130	EVVREVCSEQAETGPCRALFTRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	5.50			9.5
DD131	EVVREVCSEQAETGPCRALFKRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	7.90	2.00	1385.0	3.3
DD132	EVVREVCSEQAETGPCRAFFKRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	112.00			16.8
DD120	EVVREVCSEQAETGPCRAAFSAWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	8.30			11.0
DD121	EVVREVCSEQAETGPCRALLSAWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	19.00			21.0
BG014	EVVREVCSEQAETGPCRALIWHWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	9.20	18.70	18.0	

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FIG. 46G

DD122	EVVREVCSEQAETGPCRALIFAWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	15.00			46.0
BG015	EVVREVCSEQAETGPCRALIYHWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	6.00	12.20	19.4	597.0
BG020	EVVREVCSEQAETGPCRAAIHKWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	1.70		106.0	
BG022	EVVREVCSEQAETGPCRAAIYHWYFDVTEGKCAPFFYGGCGGNRNNFDTEEHCMAVCGSAI	0.64	7.26	14.5	
BG023	EVVREVCSEQAETGPCRALIQHWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	23.00		262.0	
BG024	EVVREVCSEQAETGPCRALIYKWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	4.10	7.47	38.7	
BG027	EVVREVCSEQAETGPCRAAIQHWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	5.80		144.0	
DD116	EVVREVCSEQAETGPCRAAIFRWYFDVTEGKCAPFFYGGCRGNRNNFDTEEYCMAVCGSAI	0.14		583.0	84.0
TW6191	EVVREVCSEQAETGPCRAAIFRWYFDVTEGKCAPFFYGGCYGNRNNFDTEEYCMAVCGSAI	0.26		664.0	20.0
DD117	EVVREVCSEQAETGPCRALIPRWYFDVTEGKCAPFFYGGCRGNRNNFDTEEYCMAVCGSAI	0.11		1034.0	99.0
BG029	EVVREVCSEQAEVGPCRALIYHWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	3.20		7.9	
BG030	EVVREVCSEQAESGPCRALIYHWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	4.60		26.1	
BG033	EVVREVCSEQAEVGPCRAAIYHWYFDVTEGKCAPFFYGGCGGNRNNFDTEEHCMAVCGSAI	0.75		5.6	

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FIG. 46H

BG034	EVVREVCSEQAESGPCRAAIYHWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	0.47		18.5	
BG040	EVVREVCSEQAEIGPCRALIYHWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	3.40		8.6	
BG016	EVVREVCSEQAETGPCRGAIQHWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	160.00		178.0	
BG017	EVVREVCSEQAETGPCRGAIRHWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	180.00		200.0	
BG021	EVVREVCSEQAETGPCRGSIRHWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	340.00		224.0	
BG025	EVVREVCSEQAETGPCRGLIYHWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	65.00		16.2	
BG026	EVVREVCSEQAETGPCRGAIYHWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	50.00		34.9	
DD118	EVVREVCSEQAETGPCRALHNRWYFDVTEGKCAPFFYGGCRGNRNNFDTEEYCMAVCGSAI	0.53			
DD134	EVVREVCSEQAETGPCRALFKRWYFDVTEGKCAPFFYGGCYGNRNNFDTEEYCMAVCGSAI	1.10	1.05	15640.0	0.6
DD135	EVVREVCSEQAETGPCRALFKRWYFDVTEGKCAPFFYGGCLGNRNNFDTEEYCMAVCGSAI	1.30		7473.0	0.9
DD136	EVVREVCSEQAETGPCRALFKRWYFDVTEGKCAPFFYGGCMGNRNNFDTEEYCMAVCGSAI	1.10			1.8

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FIG. 47

VOLUMES

NS	344.25
KPI	245.75

	KPI	NS
	298	366
	266	342
	354	294
	258	385
	168	288
	266	469
	172	338
	184	272
MEAN	245.75	344.25
STDEV	66.2414415	63.97488346
TTEST		0.009094999

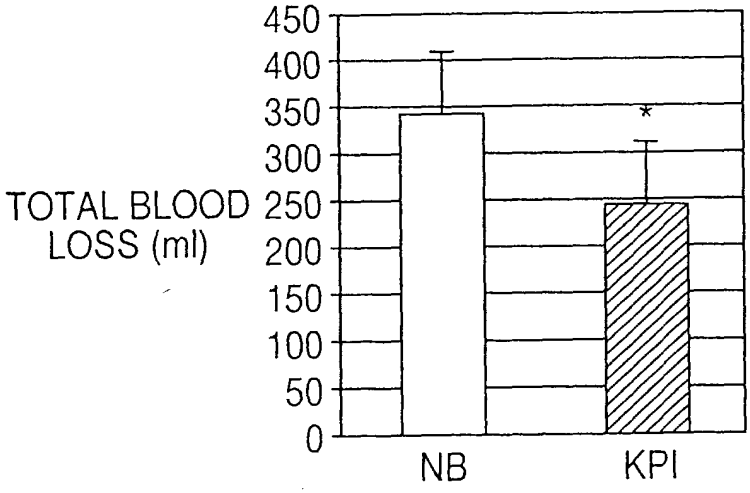

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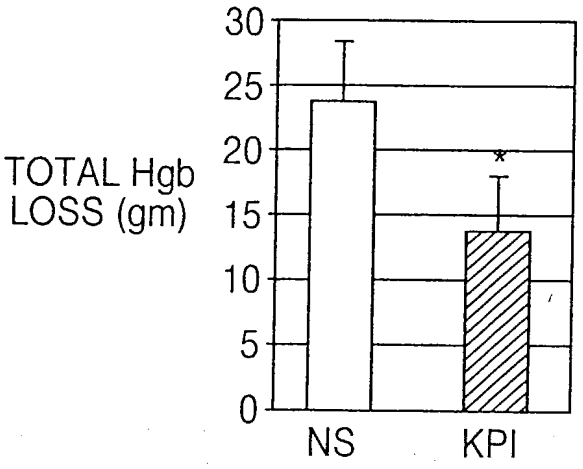
FIG. 48

HEMOGLOBIN

NS	23.61
KPI	13.59

	KPI	NS
	16.58	24.95
	15.19	24.87
	20.21	20.46
	8.99	27.59
	14.63	18.23
	15.31	31.59
	7.7	23.26
	10.14	17.96
MEAN	13.59375	23.61375
STDEV	4.261438	4.68761
TTEST		0.000536



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PaO2

FIG. 49

	Baseline PaO2		End CPB		Obs 60 min		Obs 180 min	
	KPI	NS	KPI	NS	KPI	NS	KPI	NS
	652.2	670.9	495.7	60.5	483.7	441.3		391.3
	654	559.2	444.6	132.2	330.1	448.7	264.1	484.6
	596.2	622.9	170.2	93.8	415.4	85.1	416.5	81.3
	606.2	689.2	264.2	333.9	430.2	529.6	361.9	333.2
	633.1	665.1	567.2	341.7	613	568.3	90.8	546.6
	646.6	527	507.4	226.9	564.3	438.1	518.2	485.3
	563.2	461.7	547.1	89.1	501	42.6	494.2	45.6
	659.9	508	416.6	59.7	504.5	405.8	452	383.7
MEAN	626.425	588	426.625	167.225	480.275	369.938	371.1	344
STDEV	34.4692	85.5055	140.474	117.993	88.6187	196.523	150.277	186.22
	3	6	1	1	9	5	4	7
TTEST	*p=*	*0.268*	*p=*	*0.0014*	*p=*	0.17915	*p=*	0.76
	N.S.				N.S.			

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FIG. 50

Summary of Data

	Total volume loss	Total Hgb Loss
KPI-1	298	16.58
KPI-2	266	15.19
KPI-3	354	20.21
KPI-4	258	8.99
KPI-5	168	14.63
KPI-6	266	15.31
KPI-7	172	7.7
KPI-8	184	10.14

MEAN	245.75	13.59
STDEV	66.24	4.26

NS-1A	366	24.95
NS-2	342	24.87
NS-3	294	20.46
NS-4	385	27.59
NS-5	288	18.23
NS-6	469	31.59
NS-7	338	23.26
NS-8	272	17.96

MEAN	344.25	23.61
STDEV	63.97	4.69

*$p = 0.009$ *$p = 0.0005$

Total Volumes

Chest tube	Sacrifice
185	113
198	68
142	212
190	68
96	72
188	78
134	38
158	26
274	92
236	106
252	42
303	82
140	148
261	208
218	120
206	66

Serial Chest tube Hbg

0-30min	30-60min	60-120min	120-180min
3.7	4.3	8.6	6.2
4.3	6.4	6.7	5.7
4.1	4.4	7	7.1
2.8	4	4.4	1.9
6.3	6.5	7	6.7
4.1	6.1	5.6	6.3
3.1	4.6	5.4	4.4
6.9	5.8	5.4	4.2

MEAN	4.41	5.26	6.26	5.3
STDEV	1.45	1.04	1.32	1.72

7.7	8.6	6.1	5.4
7.2	7.4	7.6	7.1
5.4	7.5	7.5	6.5
8.4	7.2	7.1	6.3
7.5	7.2	5.2	5.6
4	7	7.3	7.4
7.5	7.7	5.8	4.2
7.4	8.2	6	5.3

MEAN	6.89	7.6	6.58	6.1
STDEV	1.44	1.04	0.91	0.85

*$p = 0.004$ *$p = 0002$ *NS* *NS*

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